UNIVERSITY OF GLASGOW

A Synthesis of Theopederin D

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To Cheryl and Mum and Dad

UNIVERSITY OF GLASGOW

ABSTRACT

FACULTY OF SCIENCE

Doctor of Philosophy

A SYNTHESIS OF THEOPEDERIN D

by Christopher Smith

A stereocontrolled synthesis of 18-*O*-methyl mycalamide B (**1.5**) and theopederin D (**1.1d**) is reported in this thesis. 18-*O*-Methyl mycalamide B (**1.5**) was synthesised first and the route was adapted enabling a synthesis of theopederin D (**1.1d**) to be completed. The synthesis of theopederin D (**1.1d**) included a metallated dihydropyran approach to couple the left fragment (**1.72**) and the right fragment (**6.19**) together and a reaction between oxirane (**6.7**) and a MOM ether to forge the *cis*-2,4,7-trioxabicyclo[4.4.0]decalin ring. An efficient large scale route was developed to provide substantial quanities of early intermediates of the right fragment (**6.19**) incorporating a highly enantioselective aymmetric reduction to generate β-hydroxy ester (**4.4**) and a highly enantioselective asymmetric aldol reaction to also generate β-hydroxy ester (**4.4**). A new highly diastereoselective synthesis of the left fragment (**1.72**) was developed starting from ethyl (*S*)-lactate (**3.4**). The absolute stereochemistry of an andvanced intermediate (**6.20**) was determined by X-ray crystallography.

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Preface

The research described in this thesis was carried out under the supervision of Professor P. J. Kocienski at the University of Southampton between October 1995 and July 1997 and then at the University of Glasgow between August 1997 and September 1998. No part of this thesis has been previously submitted for a degree at this or any other university, except where specific acknowledgement has been made. Part of this thesis has been previously published:

Kocienski, P. J., Narquizian, R., Raubo, P., Smith, C., Boyle, F. T. *Synlett* **1998**, 869.
Kocienski, P. J., Narquizian, R., Raubo, P., Smith, C., Boyle, F. T. *Synlett* **1998**, 1432.

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Finally I would like to thank my wife Cheryl Smith for her support over the years and for moving from Southampton to Glasgow after only six weeks of marriage.

Abbreviations

Å	angstrom
Ac	acetyl
ADH	asymmetric dihydroxylation
AIBN	2,2'-azobis(2-methylpropionitrile)
Allyl	2-propenyl
Anal.	combustion analysis
aq	aqueous
Ar	aryl
BINAP	1,1′-bis(diphenylphosphino)-1,1'-binaphthyl
Bn	benzyl
bp	boiling point
^{n}BuLi	*n*-butyllithium
c	concentration in g/100 mL (for optical rotation)
COSY	correlation spectroscopy
CSA	camphorsulfonic acid
CI	chemical ionisation
d	days
D	dextro rotary
Δ	reflux
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]undecene-7
de	diastereomeric excess
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIAD	di*iso*-propyl azodicarboxylate
DIBAL	di*iso*-butylaluminium hydride
DMAP	4-dimethylaminopyridine
DMF	*N*,*N*′-dimethylformamide
DMPM	dimethoxyphenylmethyl
DMPU	1,3-dimethyl-3,4,5-tetrahydro-2(1*H*)-pyrimidinone
DMS	dimethyl sulfide
dr	diastereomeric ratio
er	enantiomeric ratio

EI	electron impact
eq	equivalents
ES	electrospray
Et	ethyl
g	gram
h	hours
HMBC	heteronuclear multiple quantum coherence
HMPA	hexamethylphosphoramide
HMQC	heteronuclear multiple bond correlation
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
i	*iso*
IC	inhibition constant
Im	imidazole
IR	infrared
Kg	kilogram
KHMDS	potassium hexamethyldisilazide
L	levo rotary
LAH	lithium aluminium hydride
LDA	lithium di*iso*-propylamide
LRMS	low resolution mass spectrometry
M	molarity
*m*CPBA	*meta*-chloroperbenzoic acid
Me	methyl
MEM	methyoxyethoxymethyl
mg	milligram
MHz	megahertz
min	minute
mL	millilitre
mmol	millimole
MOM	methoxymethyl
mp	melting point
Ms	methanesulfonyl
MS	molecular sieves
MTPA	α-methoxy-α-(trifluoromethyl)phenylacetic acid
n	normal
ng	nanogram
nM	nanomolar
NMR	nuclear magnetic resonance

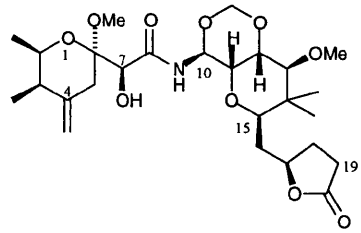
PDC	pyridinium dichromate
Ph	phenyl
Piv	pivaloyl
PMA	phosphomolybdic acid
ppm	parts per million
PPTS	pyridinium *para*-toluenesulfonate
Pr	propyl
psi	pounds per square inch
pyr	pyridine
rt	room temperature
s	secondary
SAR	structure activity relationship
SCUBA	self-contained underwater breathing apparatus
SEM	2-(trimethylsilyl)ethoxymethyl
t	tertiary
TBAF	tetrabutylammonium fluoride
TBS	*tert*-butyldimethylsilyl
TBSCN	*tert*-butyldimethylsilyl cyanide
TBSOTf	*tert*-butyldimethylsilyl triflate
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMEDA	*N*, *N*, *N'*, *N'*-tetramethylethylenediamine
TMS	trimethylsilyl
TPAP	tertrapropylammonium perruthenate
Tr	trityl
Ts	*para*-toluenesulfonyl
UV	ultraviolet

Chapter 1

A Review of the Literature Relating to Theopederin D

1.1 Structure and Isolation of Theopederin D

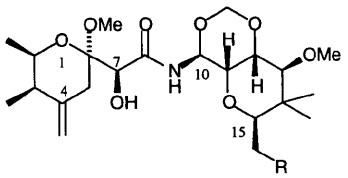
Theopederin D **1.1d** (scheme 1.1), was isolated from a marine sponge of the genus *Theonella*. Specimens of the sponge were collected using SCUBA off Hachijo-jima Island 300 km south-east of Tokyo. The structure of theopederin D **1.1d** was elucidated at the time of isolation by a combination of mass spectroscopy, infra-red spectroscopy and nuclear magnetic resonance techniques including COSY, HMQC and HMBC[1] .



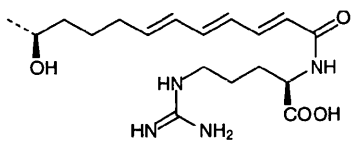
1.1d Theopederin D

Scheme 1.1

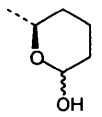
The spectral features of theopederin D were reminiscent of mycalamide A[2] and B[3] (**1.3** and **1.4**) and onnamide A **1.2**,[4] which are heterocyclic compounds from marine sponges *Mycale* and *Theonella* respectively (scheme 1.2). Comparison of the NMR spectroscopic data revealed that theopederin D contained the O1-C16 portion of the mycalamide skeleton and connectivities from H-16 to H-19 were observed from the COSY spectrum and an IR absorption at 1765 cm^{-1} indicated the presence of a butyrolactone, thus defining the structure of theopederin D. A range of five theopederins (A-E, **1.1a-1.1e**)[1] were isolated from the sponge *Theonella* whose structures were determined in a similar way to theopederin D. Interestingly all of the theopederins, mycalamides and onnamide A are closely related to the insect toxin pederin **1.6** (scheme 1.2) which was isolated in 1952 from the blister beetle *Paederus fuscipes* [5]and whose structure was determined some 16 years later[6] after some elegant degradation studies[7]. The occurrence of such closely related compounds from such taxonomically remote animals as sponges and beetles may indicate the connection of a common precursor, possibly a symbiotic micro-organism[8] .



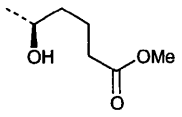
1.1 a-e



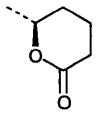
1.2 Onnamide A



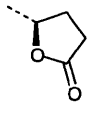
1.1a
Theopederin A



1.1b
Theopederin B

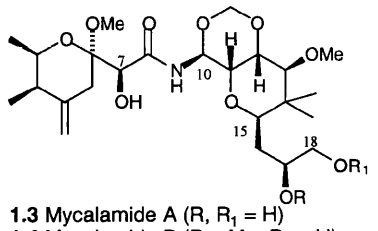


1.1c
Theopederin C

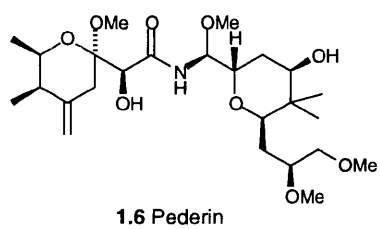


1.1d
Theopederin D

1.1e R = OH Theopederin E



1.3 Mycalamide A (R, R_1 = H)
1.4 Mycalamide B (R = Me, R_1 = H)
1.5 18-*O*-Methyl Mycalamide B (R, R_1 = Me)



1.6 Pederin

Scheme 1.2

1.2 Biological Evaluation

The biological evaluation of theopederin D (**1.1d**) has been hindered due to the small quantities available, allowing only a single piece of data to be collected; theopederin D was shown to be markedly cytotoxic against P388 murine leukemia cells with an IC_{50} of 1.0 ng/mL.[1] There was however a more thorough biological evaluation of the mycalamides and due to their structural similarity to theopederin D (**1.1d**), it would be reasonable to assume a similar biological mode of action for theopederin D (**1.1d**) as for the mycalamides. Therefore it is relevant to mention the biological evaluation of the mycalamides in this thesis.

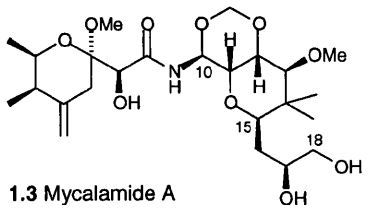
Mycalamides A and B (**1.3** and **1.4**) reveal potent *in vitro* cytotoxicity and *in vivo* antitumor efficacy against several leukemia and solid tumour model systems. Both mycalamide A and B (**1.3** and **1.4**) inhibited the replication of cultured murine lymphoma P388 cells at extremely low concentrations (P388 IC_{50}'s 0.7 ± 0.3 $ngcm^{-3}$ and 3.0 ± 1.3 $ngcm^{-3}$ respectively). Furthermore, both inhibited HL-60, HT-29 and A549 human tumour cell replication IC_{50} < 5 nM and were active against P388 leukemia. Mycalamide A (**1.3**)

increased the life span of mice carrying ascitic lymphomas and a variety of ascitic and solid tumours.[9]

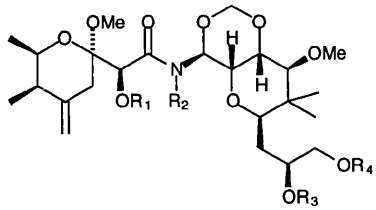
The mycalamides also reveal antiviral activity[10] and a recent biological investigation of mycalamide A and analogues[11] showed that 10-*epi*-mycalamide A and 7-*epi*-10-*epi*-mycalamide A displayed potent antiviral activity against VZV (Varicella-zoster virus, TR's of 8 and <32 respectively) and low cytotoxicity against HEL cells (IC_{50}'s = 12.5 and >50.0 μgcm^{-3} respectively). The results are significant because they show a structure activity relationship (SAR) for mycalamide A against viruses which is in the opposite sense to the SAR against tumours with regard to the C-7 and C-10 stereogenic centres.

In addition mycalamide A blocks T-cell activation in mice and is a 1000-fold more potent than cyclosporin A in this model.[12]

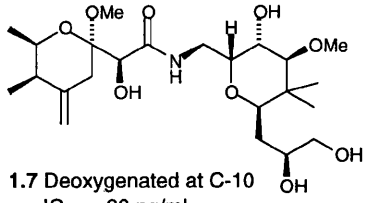
SAR data for the cytotoxicity of the mycalamides against P388 leukemia cells, has been reported from a microscale derivatisation study using natural supplies of mycalamide[13-15]. These experiments demonstrated that the α-hydroxyamido acetal functionality is essential for the *in vitro* P388 anti-leukemia activity. Acylation or alkylation of the 7-OH group resulted in the formation of derivatives with a 10–100-fold lower bioactivity. Methylation of both the amide nitrogen and the 7-OH caused a 1000-fold decrease in the bioactivity. Cleavage of the C8-N9 amide bond resulted in a total loss of biological activity. The product of deoxygenation at C-10 (**1.7**) was 40 times less bioactive than mycalamide A, suggesting the critical importance of the C-10 centre. Further evidence was provided by Kocienski and co-workers showing the C-10 epimer to be 10^3-fold less active than the natural parent compound[16]. The microscale studies also demonstrated that *O*-methylation at C-18 of mycalamide B (**1.4**) gave increased bioactivity against P388 leukemia cells with an IC_{50} of 0.07 ng/mL. Thus, 18-*O*-methyl mycalamide B **1.5** possess the same potency as pederin **1.6** against P388 leukemia cells. Kocienski and co-workers synthesised 18-*O*-methyl mycalamide B[17] **1.5** and also showed that its inhibition of DNA synthesis (IC_{50} = 0.80 nM) and protein synthesis (IC_{50} = 1.65 nM) were similar to that of pederin (IC_{50} = 0.85 nM and 1.84 nM respectively)[16]. A summary of the cytotoxicity data is given in scheme 1.3.



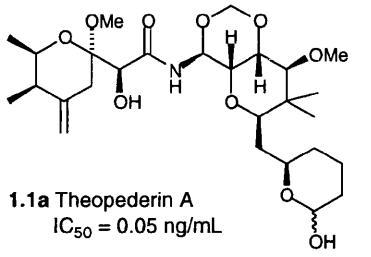
1.3 Mycalamide A
IC_{50} = 0.5 ng/mL



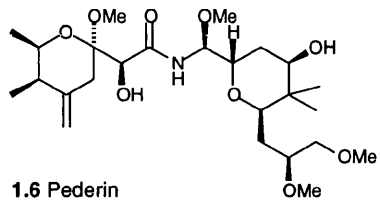
R_1, R_2, R_3, R_4 = H Unless stated otherwise	IC_{50} ng/mL
R1 = Me	80
R_1, R_2 = Me	1000
R_3 = Me	0.1
R_3 = R_4 = Me	0.07
R_1 = COMe, R_3 = Me	2
R_1 = COC_6H_4Br	23



1.7 Deoxygenated at C-10
IC_{50} = 20 ng/mL



1.1a Theopederin A
IC_{50} = 0.05 ng/mL



1.6 Pederin
IC_{50} = 0.07 ng/mL

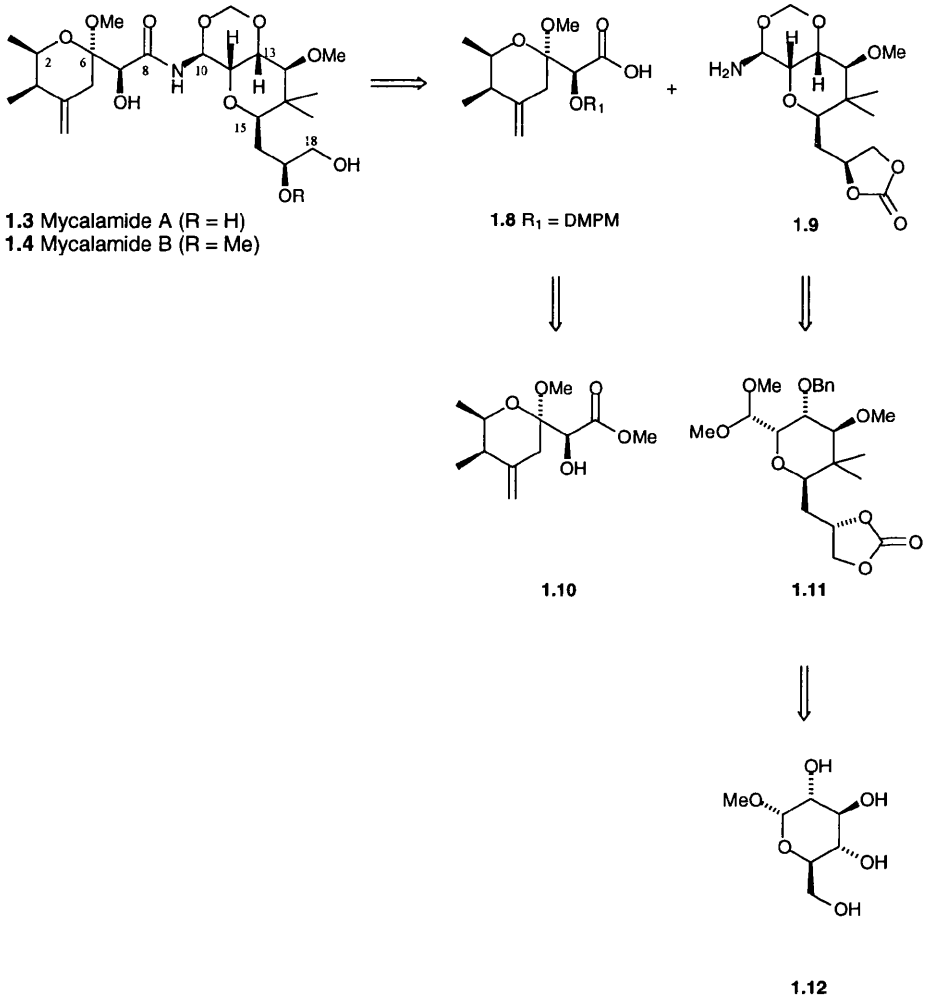
Scheme 1.3

1.3 A Summary of the Synthetic Approaches Towards the Mycalamides

There are no synthetic studies towards the theopederins A-E (**1.1a-e**) reported in the literature to date, however there has been substantial work published regarding the synthesis of the related mycalamides[17-28], onnamide A (**1.2**)[29] and pederin (**1.6**)[30-36] over a period of 21 years to date. For our purposes we will only discuss the publications directed towards the mycalamides and onnamide A but wish to advise the reader that many lessons were learned during the synthesis of pederin and that they were applied (where necessary) to the synthesis of the mycalamides. We will not discuss every publication directed towards the mycalamides but will concentrate on those which are the most relevant to our work. There have been five authors who have made substantial contributions to the synthesis of the mycalamides, they are; Yoshito Kishi[19,29], William Roush[25-28], Reinhard Hoffmann[18,20,21], Tadashi Nakata[11,23,24] and Philip Kocienski[17,22]. We will discuss the central contribution made by Kishi, Roush, Hoffmann and Kocienski relating to the synthesis of the mycalamides and onnamide A. A synthesis of mycalamide A (**1.3**) by Nakata[24] was omitted from this discussion for it was similar to that described by Kishi.[19]

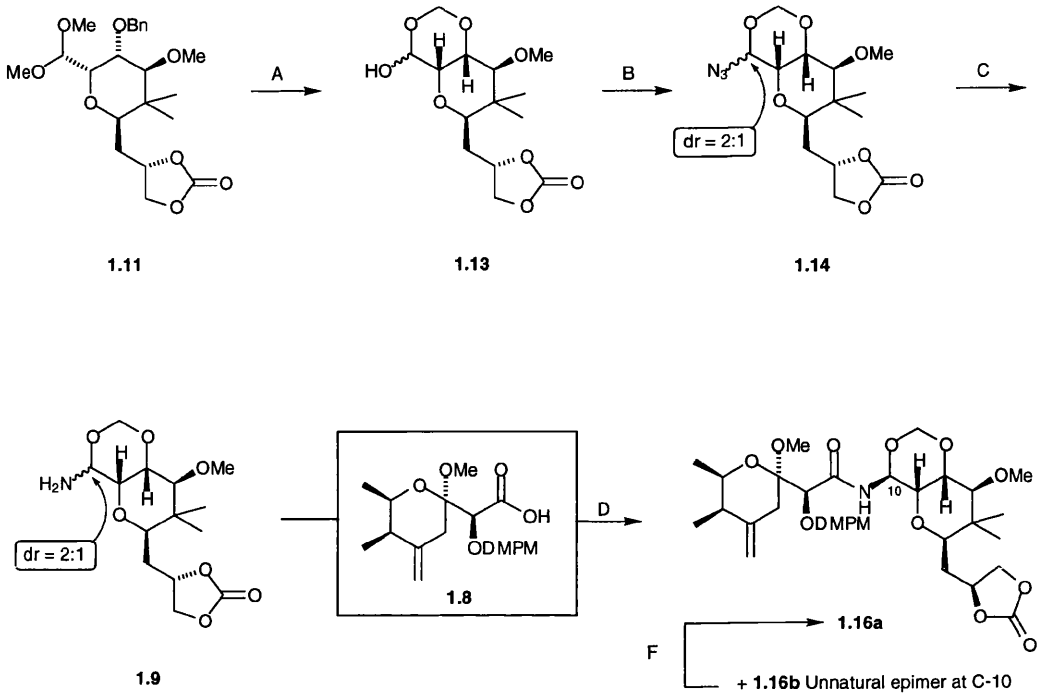
1.3a Yoshito Kishi

Yoshito Kishi reported the first synthesis of mycalamides A and B in 1990, which unambiguously defined their absolute stereochemistry.[19] Kishi chose to disconnect across the C8-N9 bond splitting mycalamide into two fragments **1.8** and **1.9** (scheme 1.4). The left fragment **1.8** was prepared in two steps from an advanced intermediate **1.10** from Nakata's synthesis of pederin[33,34]. The right fragment **1.9** was prepared by an extensive elaboration of methyl α-D-glucopyranoside **1.12** *via* the methoxy acetal **1.11**. The transformation of **1.12** to **1.11** will not be discussed for the synthesis of **1.11** was improved during Kishi's synthesis of Onnamide A.[29]



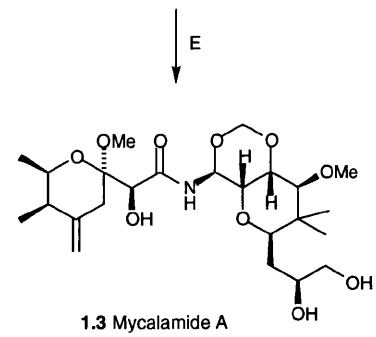
Scheme 1.4

Conversion of **1.11** to mycalamide A and mycalamide B is shown in scheme 1.5.

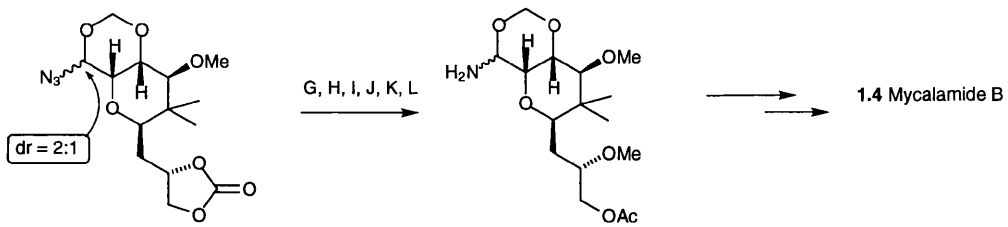


Scheme 1.5 *Reagents and conditions:*

A	86%	a) H_2, $Pd(OH)_2$ on C, EtOAc, rt; b) HCHO, HCl, 0°C
B	72%	a) MsCl, NEt_3, DMAP, CH_2Cl_2, –60°C
		b) $^nBu_4NN_3$, CH_2Cl_2, –78°C→ rt
C	↓	H_2, Pd on C, EtOAc, rt
D	78%	*p*TsCl, DMAP, CH_2Cl_2, rt
E	60%	a) ^{t}BuOK, THF, rt b) DDQ, H_2O
F	-	a) ^{t}BuOK, THF, Δ
G	–	NaOH aq, dioxane, rt
H	–	4-$MeOC_6H_4$-$(C_6H_5)_2CCl$, $(^iPr)_2NEt$, CH_2Cl_2, rt
I	–	MeI, NaH, DMF, 75°C
J	–	PTSA, MeOH, rt
K	76%	Ac_2O, DMAP, CH_2Cl_2, rt
L	↓	H_2, Pd on C, EtOAc, rt



1.3 Mycalamide A

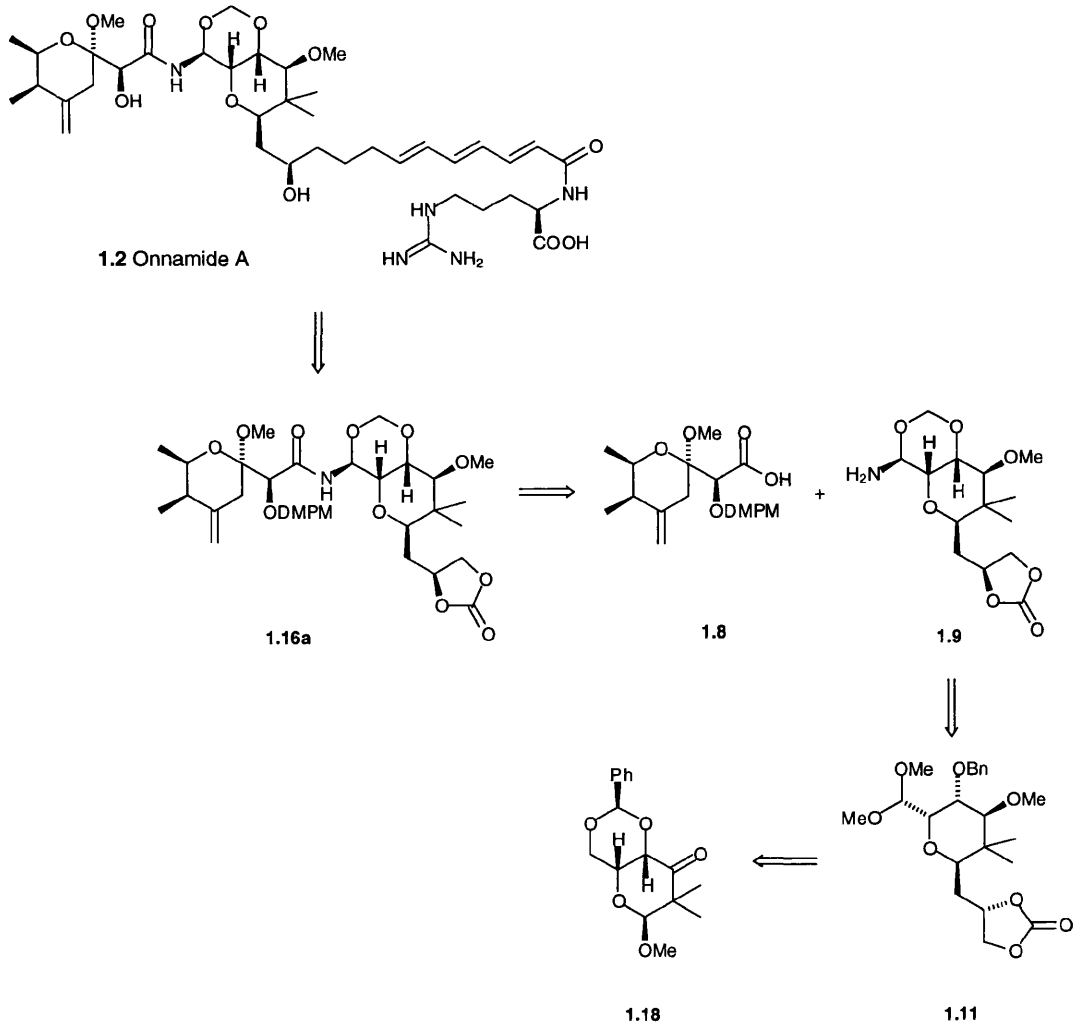


1.14 **1.17**

The benzyl protecting group in **1.11** was removed by catalytic hydrogenation followed by treatment with paraformaldehyde/$HCl_{(g)}$ to return the hemiacetal **1.13**. Standard transformations converted hemiacetal **1.13** to the azide **1.14** in 72% yield as a 2:1 mixture of inseparable diastereoisomers, a suitable precursor for mycalamide A. Conversion of the azide

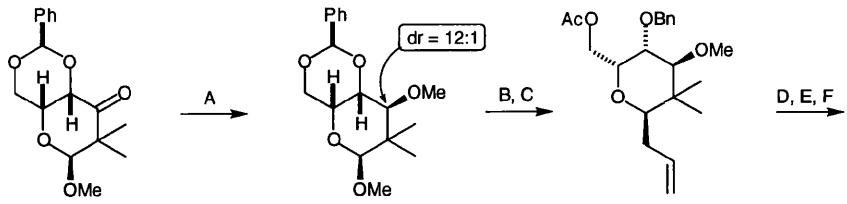
1.14 to the azide acetate **1.17** returned a suitable intermediate for the synthesis of mycalamide B in five steps. Hydrogenation of the azide **1.14** gave the expected aminal **1.9** and ^{1}H NMR spectroscopy determined a 2:1 mixture of diastereoisomers at C-10 under basic or neutral conditions and a 1:4 mixture of diastereoisomers disfavouring the natural configuration under acidic conditions. The experiments determined the stereochemistry at C-10 should be addressed at the step of amide bond formation or thereafter. The coupling of the two fragments (**1.8** and **1.9**) was achieved by activating the carboxylic acid **1.8** with TosCl and adding **1.9** to give **1.16a** (38%) and **1.16b** (40%). Epimerisation of **1.16b** to **1.16a** using base (^{t}BuOK/THF/reflux) occurred smoothly to give exclusively the natural epimer. Finally two deprotection steps then released Mycalamide A. Mycalamide B was obtained from **1.14** using the same chemistry as described above, but the epimerisation of the unnatural epimer at C-10 to the natural epimer interestingly only gave a 1:1 mixture of epimers.

In 1991 Kishi reported the first synthesis of onnamide A, once again unambiguously defining the absolute stereochemistry of the molecule.[29] The synthesis employed an intermediate **1.16a** and a disconnection strategy (scheme 1.6) which were common to a previous synthesis of mycalamide A[19].

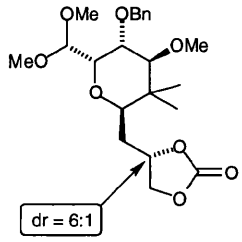


Scheme 1.6

After a synthesis of mycalamide A[19] Kishi acknowledged the synthesis of dimethoxy acetal **1.11** from methyl α-D-glucopyranoside **1.12** (scheme 1.4) was limiting due to its length and therefore developed a new synthesis of **1.11** from the known ketone **1.18** which is shown in scheme 1.7[37]. Stereoselective reduction[38] of **1.18** and *O*-methylation generated **1.19**. Standard transformations converted **1.19** to its bis-acetate and a terminal olefin was introduced by an axially selective Lewis acid-mediated allyltrimethylsilane C-glycosidation at the anomeric C-15 position to return **1.20**.[39] Asymmetric dihyroxylation[40] of olefin **1.20** followed by diol protection, acetate hydrolysis, Swern oxidation[41] and acetalisation gave **1.11**.



1.18 1.19 1.20

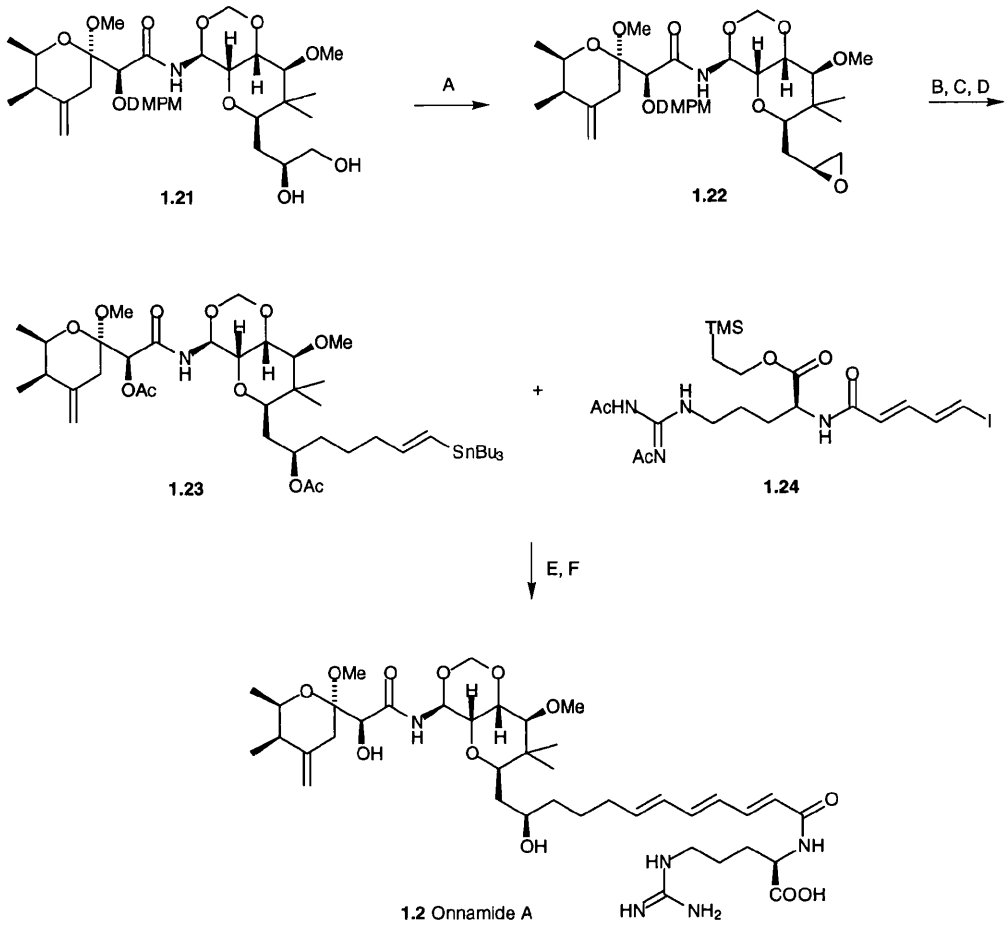


1.11

Scheme 1.7 *Reagents and conditions:*

A 78% a) $NaBH(OAc)_3$, $CeCl_3$, MeOH, 0°C; b) MeI, NaH, THF, rt
B 75% a) LAH, $AlCl_3$, Et_2O-CH_2Cl_2, Δ; b) Ac_2O, BF_3•OEt_2, rt
C 93% Trimethylallylsilane, TMSOTf, BF_3•Et_2O, MeCN, 0°C
D 65% OsO_4, N,N'-bis(2,4,6-trimethylbenzyl)-5,5)-1,2-diphenyl-1,2-diaminoethane, CH_2Cl_2, –90°C
protect as carbonate (reagents not specified)
E ↓ PTSA, MeOH, Δ
F 84% a) Swern oxidation; b) $(MeO)_3CH$, PTSA, MeOH, 0°C→rt

1.11 was converted to the diol **1.21** (scheme 1.8) using steps previously described (Scheme 1.5, steps A-Ea). The elaboration at C-18 of the diol **1.21** is shown in scheme 1.8 and is particularly relevant to our synthesis of theopederin D. **1.21** was converted to its corresponding epoxide **1.22** which was opened by a mixed cuprate prepared from $TMSCCCH_2CH_2Li$ and lithium 2-thienylcyanocuprate to give a silylacetylene which was converted to stannane **1.23**. Stille coupling[42] with the δ-iodo amide **1.24**, isomerisation to the *trans*, *trans*, *trans*, product and removal of protecting groups returned onnamide A.



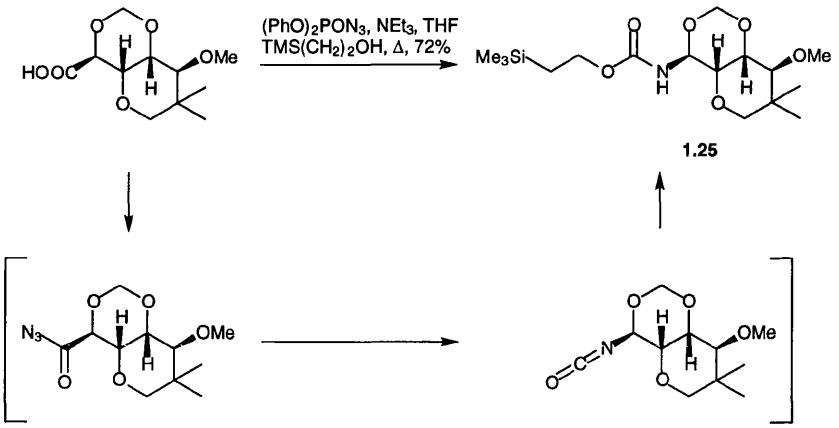
Scheme 1.8 *Reagents and conditions:*

A 85% *p*-TsIm, NaH, Imidazole, THF, 0°C →rt
B 78% a) $TMSCCCH_2CH_2Li$, lithium-2-thienylcyanocuprate, −30°C→rt; b) acetylate
C 85% DDQ, CH_2Cl_2, phosphate buffer, pH 7, rt
D 76% a) Ac_2O, NEt_3, CH_2Cl_2; b) TBAF, THF, rt; c) ^nBuSnH, AIBN, C_6H_6, Δ
E 51% a) $Pd(PPh_3)_4$, DMF, rt; b) I_2, CH_2Cl_2, rt
F 59% a) TBAF, THF, rt; b) LiOH, MeOH, rt

The syntheses of mycalamides A and B and onnamide A by Kishi[19,29] were pioneering, confirming the absolute stereochemistry of these molecules. Kishi also showed that in the closing stages of any synthesis towards the mycalamides or onnamide A acidic conditions should be avoided. The generation of the C-10 stereogenic centre was also highlighted as problematic showing that poor diastereocontrol was achieved when proceeding *via* aminal intermediate **1.17** and Kishi suggested an alternative approach may prove more efficient[19].

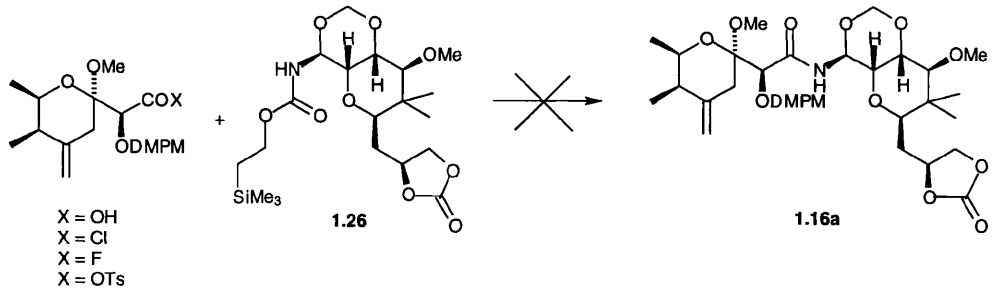
1.3b William Roush

In 1993 Roush published a new, highly diastereoselective synthesis of the trioxadecalin ring system[25] of the mycalamides A and B. The key feature of the synthesis was the use of a Curtius rearrangement[43] to install the C-10 aminal stereogenic centre as a carbamate derivative **1.25** as shown in Scheme 1.9.



Scheme 1.9

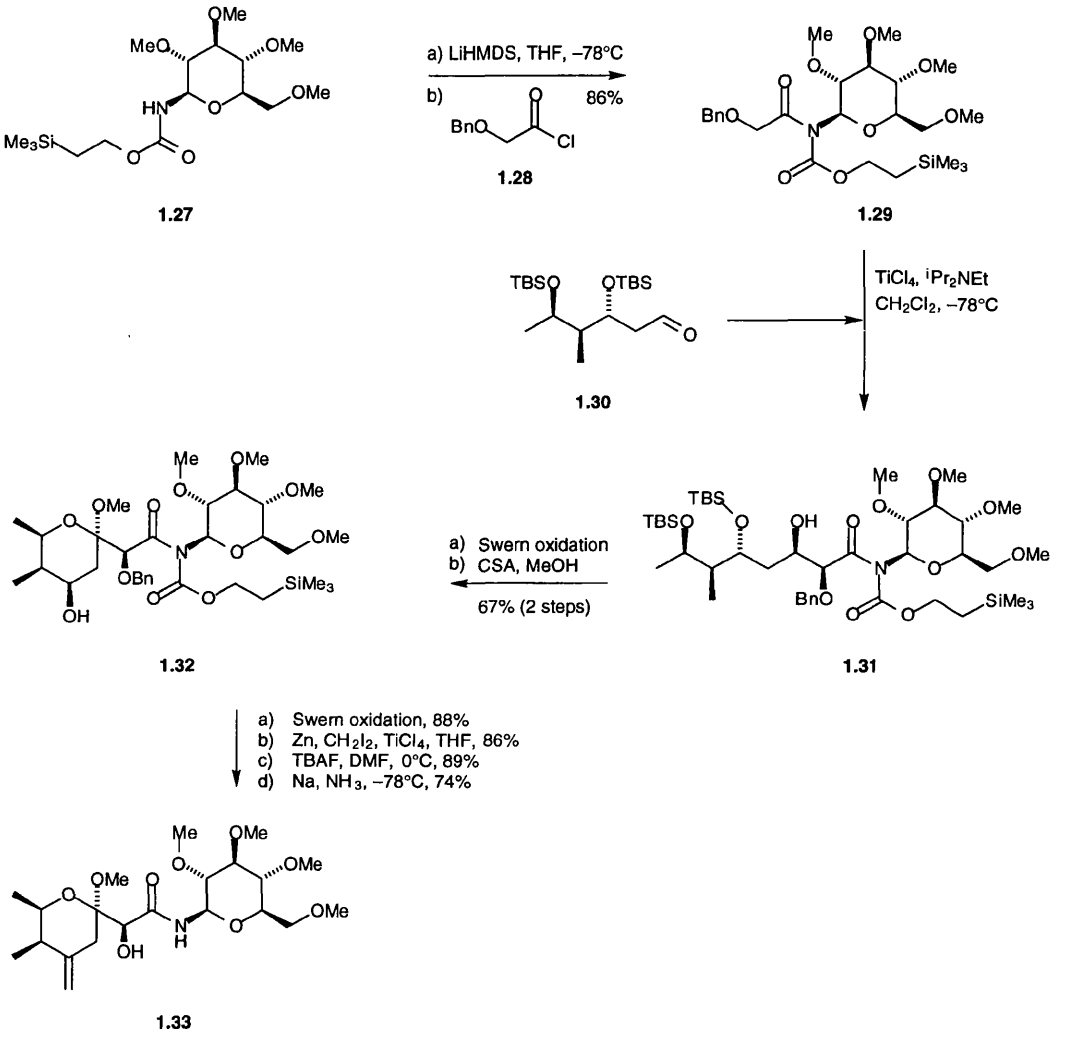
Roush anticipated completing the synthesis of mycalamide A by way of *N*-acylation[27] of carbamate **1.26**[44] with a suitable active ester of pederic acid[26], however after repeated attempts employing a wide range of conditions none of the desired coupling product was observed. A summary of the attempts is shown in scheme 1.10.



Scheme 1.10

Despite the setback described in scheme 1.10 a workable synthesis was developed. Due to exhausted supplies of right fragment **1.26** an *N*-glucosyl pederamide derivative **1.33** was prepared (scheme 1.11). The imide **1.29** was prepared by *N*-acylation of **1.27** with benzyloxyacetyl chloride **1.28** which underwent a $TiCl_4$-mediated aldol condensation[45] with aldehyde **1.30** [46]providing alcohol **1.31** as a single diastereoisomer. The excellent diastereoselectivity of the aldol reaction appears to be due to the tendency of β-alkoxy aldehydes to favour the generation of 1,3-*anti* products[47] and not due to a high

diastereofacial bias on the part of the metal enolate.[48] Swern oxidation[41] followed by treatment of β-keto imide with MeOH and camphorsulphonic acid returned the hemiketal unit **1.32**. Swern oxidation followed by the Takai-Nozaki[49] protocol introduced the *exo*-methylene unit. Finally, removal of the Teoc and benzyl ether protecting groups gave the *N*-glycosylpederamide **1.33**. Efforts to use this procedure to synthesise mycalamide A are on going.

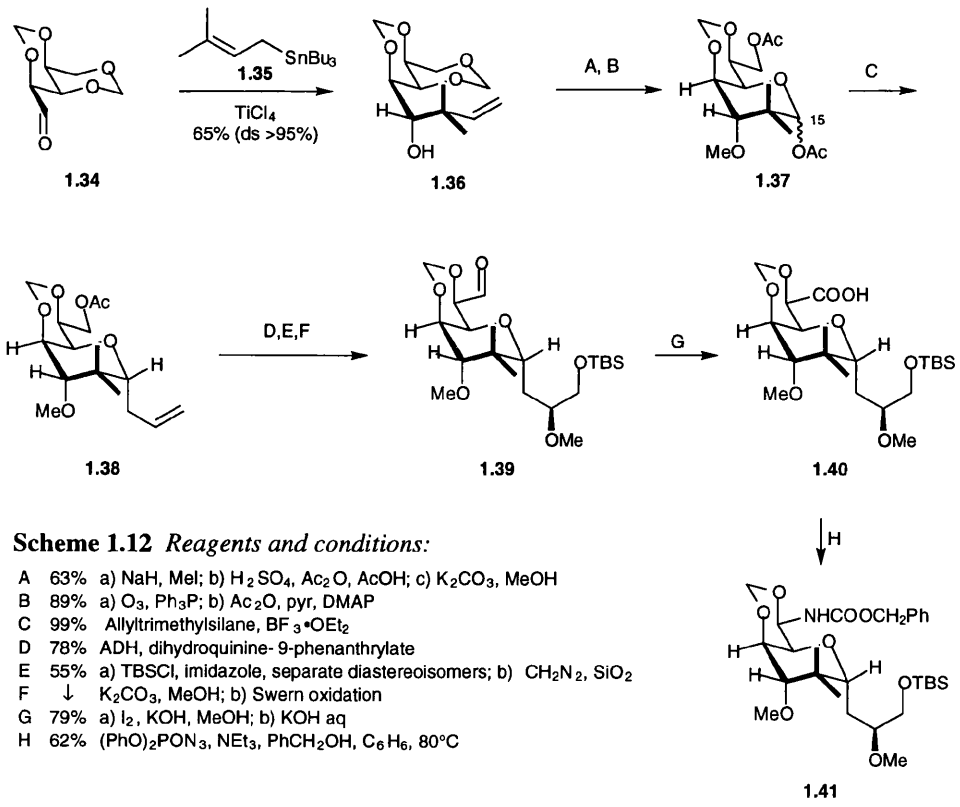


Scheme 1.11

In 1997 Roush published a new approach to pederic acid **1.8**[26] but in view of the above discussion which demonstrated that pederic acid could not be used to synthesise mycalamide A we will not discuss the route in this thesis.

1.3c Reinhard Hoffmann

Hoffmann published an approach to the trioxadeclin ring system of the mycalamides A and B in 1993[20] which was similar to that of Roush[25], in that it included a Curtius rearrangement[43] to form the C-10 aminal diastereoselectively. Hoffmann however, planned to prepare the unnatural configuration at C-10 to allow a shorter more concise route and then epimerise the C-10 stereogenic to the natural configuration towards the end of the synthesis. A summary of the route is shown in scheme 1.12.



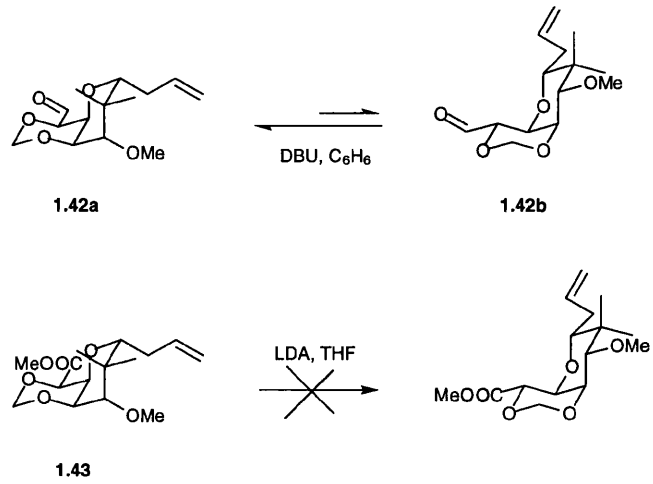
Scheme 1.12 *Reagents and conditions:*

A 63% a) NaH, MeI; b) H_2SO_4, Ac_2O, AcOH; c) K_2CO_3, MeOH
B 89% a) O_3, Ph_3P; b) Ac_2O, pyr, DMAP
C 99% Allyltrimethylsilane, $BF_3 \cdot OEt_2$
D 78% ADH, dihydroquinine- 9-phenanthrylate
E 55% a) TBSCl, imidazole, separate diastereoisomers; b) CH_2N_2, SiO_2
F ↓ K_2CO_3, MeOH; b) Swern oxidation
G 79% a) I_2, KOH, MeOH; b) KOH aq
H 62% $(PhO)_2PON_3$, NEt_3, $PhCH_2OH$, C_6H_6, 80°C

Scheme 1.12

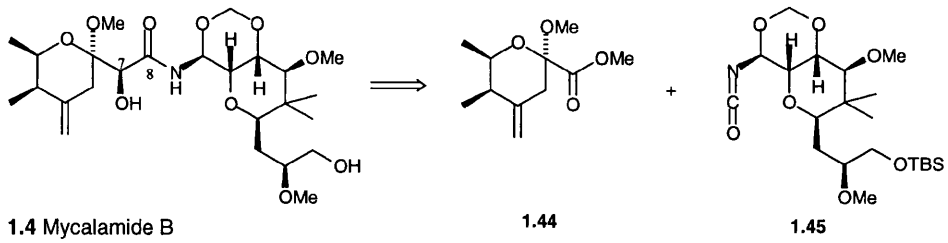
The addition of tributylprenylstannane **1.35** to the known aldehyde **1.34**[50,51] (scheme 1.12) gave alcohol **1.36** with good diastereoselectivity (de = 95%). Alcohol **1.36** was converted to the lactol acetates **1.37** in 5 steps which, followed by a stereoselective Lewis acid-mediated allylation[52] to introduce the C-15 side chain, returned **1.38**. Standard transformations gave the carboxylic acid **1.40**, a suitable precursor for the Curtius rearrangement. The Curtius rearrangement was initiated with diphenyl phoshoryl azide[53] followed by thermolysis of the acyl azide and trapping of the intermediate isocyanate with benzyl alcohol to furnish carbamate **1.41** as a single diastereoisomer.

To synthesise mycalamide B Hoffmann proposed to epimerise the C-10 stereogenic centre of aldehyde **1.42a** to the natural configuration **1.42b** (scheme 1.13), thus benefiting from the choice of starting material **1.34**, which allowed an efficient elaboration of the bicyclic framework. However, all attempts failed suggesting the equilibrium between **1.42a** and **1.42b** may lie on the side of **1.42a**.[18]



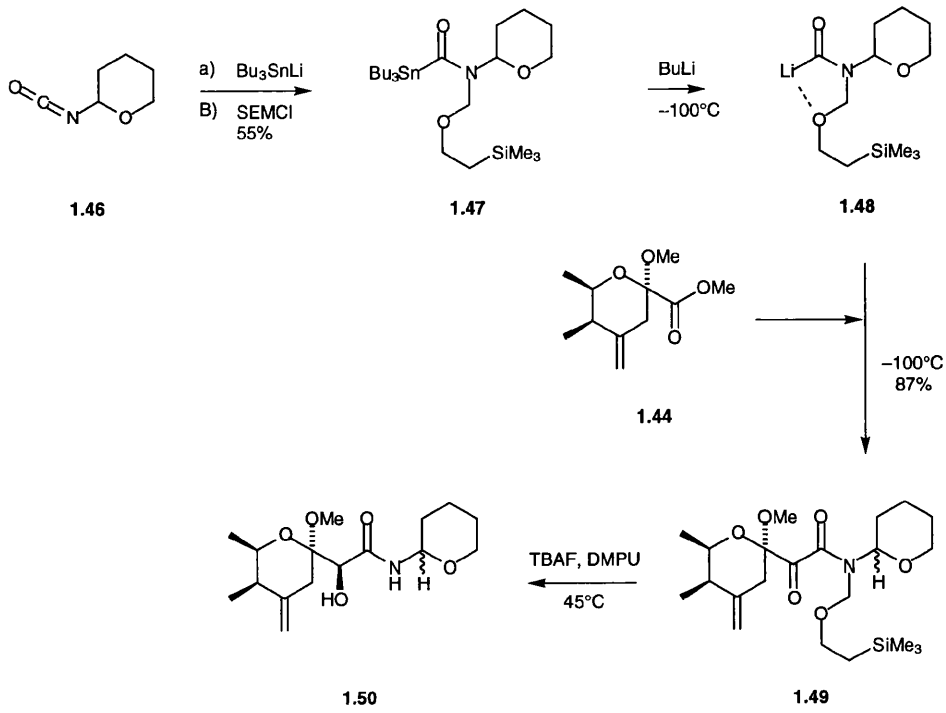
Scheme 1.13

Then in 1996 Hoffmann proposed a novel strategy[21] to construct the *N*-acyl aminal bridge of Mycalamide B. He chose to disconnect mycalamide B across the C7-C8 bond giving rise to ester **1.44** and isocyanate **1.45** as left and right fragments respectively, Scheme 1.14.



Scheme 1.14

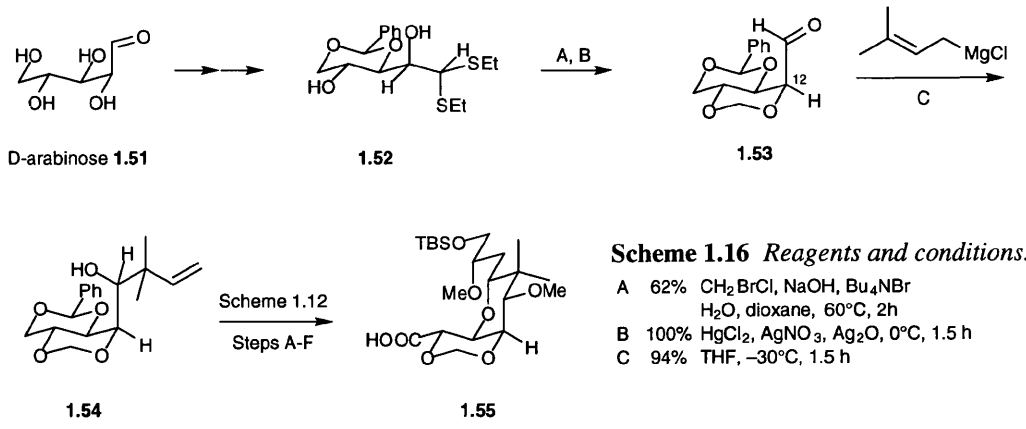
The feasibility of the approach, shown in scheme 1.14, was successfully demonstrated in a model study,[21] scheme 1.15.



Scheme 1.15

Commercially available isocyanate **1.46** upon treatment with Bu_3SnLi followed by quenching with [2-(trimethylsilyl)ethoxy]methyl chloride (SEMCl) furnished **1.47** in 55% yield. The use of SEM for protection of the N-atom was a judicious choice, stabilising the formation of the lithio derivative **1.48** at low temperature. Generation of **1.48** in the presence of ester **1.44** gave **1.49** in 87% yield. Treatment of **1.49** with TBAF and DMPU removed the SEM group with concomitant reduction the keto function to return **1.50** with the C7-OH moiety, present in the mycalamides in a 3:1 ratio. The origin of the hydride for the reduction of the keto function is unknown.

In order to adopt the new approach shown in scheme 1.15 to prepare mycalamide B, carboxylic acid **1.55** with the natural configuration at the C-10 aminal had to be synthesised. Failure to epimerise **1.42a** to **1.42a** (scheme 1.13) caused Hoffmann to devise a new synthesis of **1.55** this time starting from benzylidene acetal **1.52** derived from D-arabinose **1.51**,[54] scheme 1.16.



Scheme 1.16 *Reagents and conditions:*

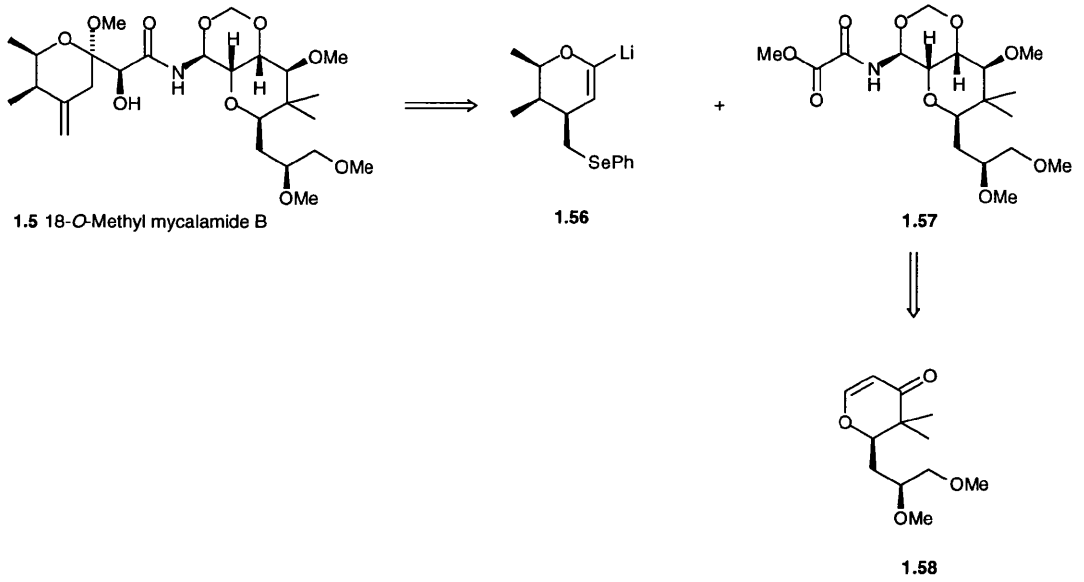
A 62% CH_2BrCl, NaOH, Bu_4NBr
H_2O, dioxane, 60°C, 2h
B 100% $HgCl_2$, $AgNO_3$, Ag_2O, 0°C, 1.5 h
C 94% THF, –30°C, 1.5 h

Scheme 1.16

Methylenation of benzylidene acetal **1.52** under basic conditions[55-57] and subsequent hydrolysis of the dithioacetal moiety returned the aldehyde **1.53** in 62% yield. Chelation controlled ($MgBr_2$) addition of prenylmagnesium chloride gave the desired homoallylic alcohol **1.54** as a single diastereoisomer. Conversion of **1.54** to the carboxylic acid **1.55** followed the route developed in the C-10-epi series shown in scheme 1.12 (steps A-F). The completion of Mycalamide B has not yet been reported.

1.3d Philip Kocienski

In 1996 Kocienski reported a synthesis of 18-*O*-methyl mycalamide B **1.6**[17] based upon the use of a metallated dihydropyran approach developed during a synthesis of pederin **1.4**.[36] A retrosynthetic analysis is shown in scheme 1.17. The lithiated dihydro-2*H*-pyran **1.56** was prepared as described during a synthesis of pederin[36] and oxalamide **1.57** was prepared from the enone **1.58** which was also previously reported after a synthesis of pederin.[31,36]



1.5 18-*O*-Methyl mycalamide B

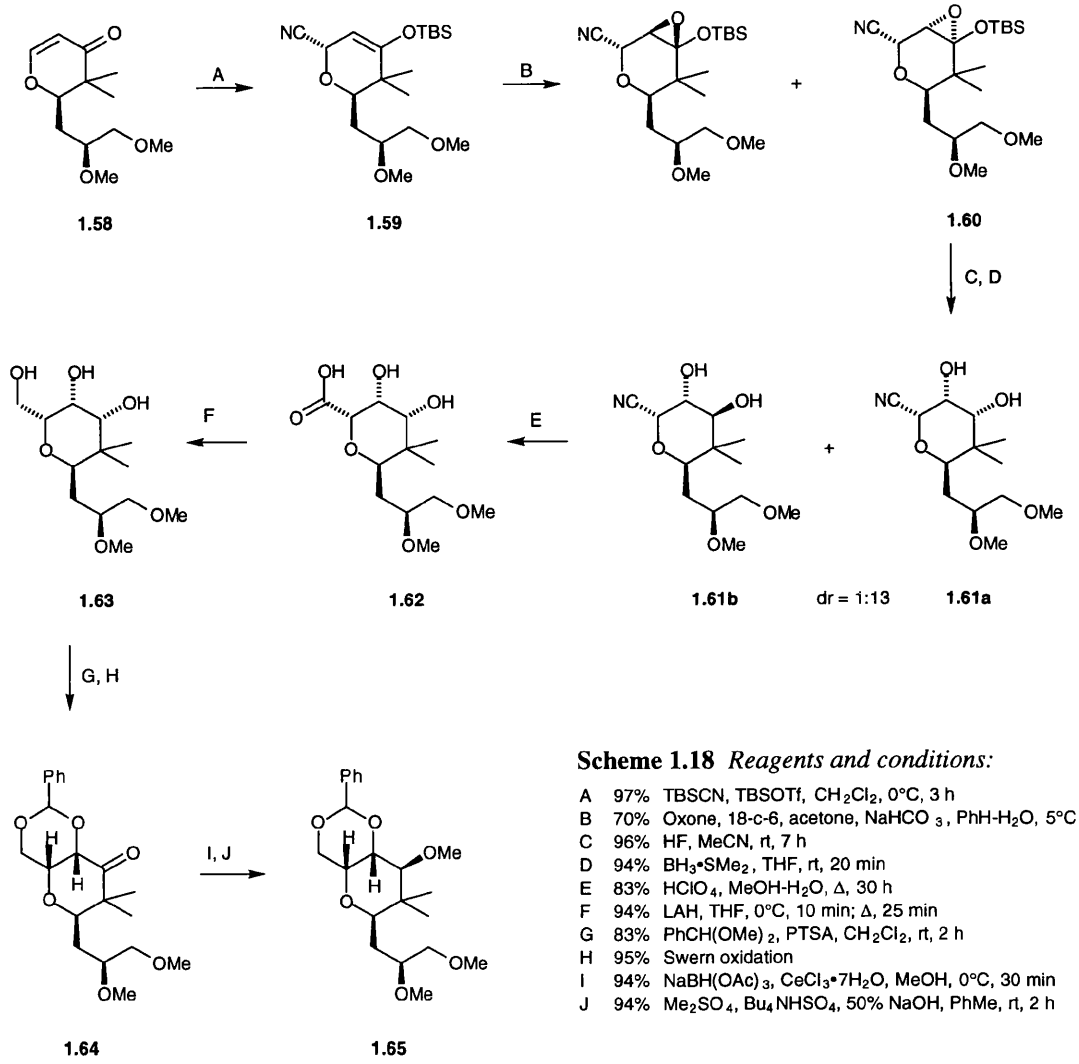
1.56

1.57

1.58

Scheme 1.17

Conversion of enone **1.58** to **1.65** is shown in scheme 1.18.

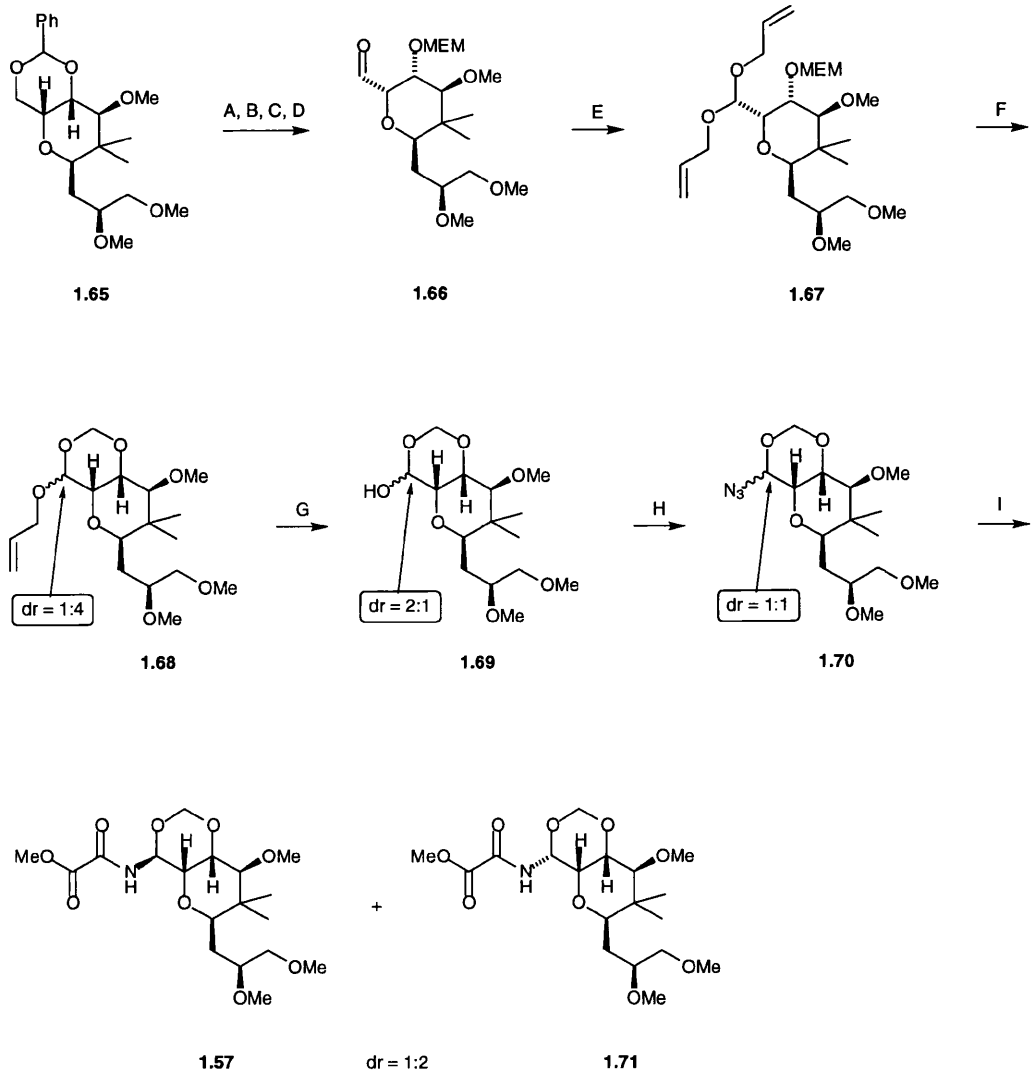


Scheme 1.18 *Reagents and conditions:*

A	97%	TBSCN, TBSOTf, CH_2Cl_2, 0°C, 3 h
B	70%	Oxone, 18-c-6, acetone, $NaHCO_3$, PhH-H_2O, 5°C
C	96%	HF, MeCN, rt, 7 h
D	94%	BH_3•SMe_2, THF, rt, 20 min
E	83%	$HClO_4$, MeOH-H_2O, Δ, 30 h
F	94%	LAH, THF, 0°C, 10 min; Δ, 25 min
G	83%	$PhCH(OMe)_2$, PTSA, CH_2Cl_2, rt, 2 h
H	95%	Swern oxidation
I	94%	$NaBH(OAc)_3$, $CeCl_3$•$7H_2O$, MeOH, 0°C, 30 min
J	94%	Me_2SO_4, Bu_4NHSO_4, 50% NaOH, PhMe, rt, 2 h

Conjugate addition of TBSCN to enone **1.58** in the presence of TBSOTf gave the cyano-TBS enol ether **1.59** with very high 1,3-asymmetric induction. Epoxidation of **1.59** with dimethyldioxirane[58-60] gave a 3.5:1 mixture of diastereoisomers in favour of the desired epoxide **1.60**. After separation of the diastereoisomers by column chromatography, hydrolysis and reduction of the ketone returned a mixture of diols **1.61a,b** in an unfavourable ratio of 13:1 at C-13. The mixture, on treatment with perchloric acid in aqueous MeOH, transformed **1.61a** exclusively to the ester **1.62**. After reduction of **1.62**, the triol **1.63** was converted to its benzylidene acetal before Swern oxidation[41] furnished the ketone **1.64**. A highly diastereoselective reduction[38] of **1.64** and *O*-methylation returned the crystalline methyl ether **1.65** in 88% yield (2 steps).

The transformation of **1.65** to the oxalamides **1.57** and **1.71** is shown in scheme 1.19.



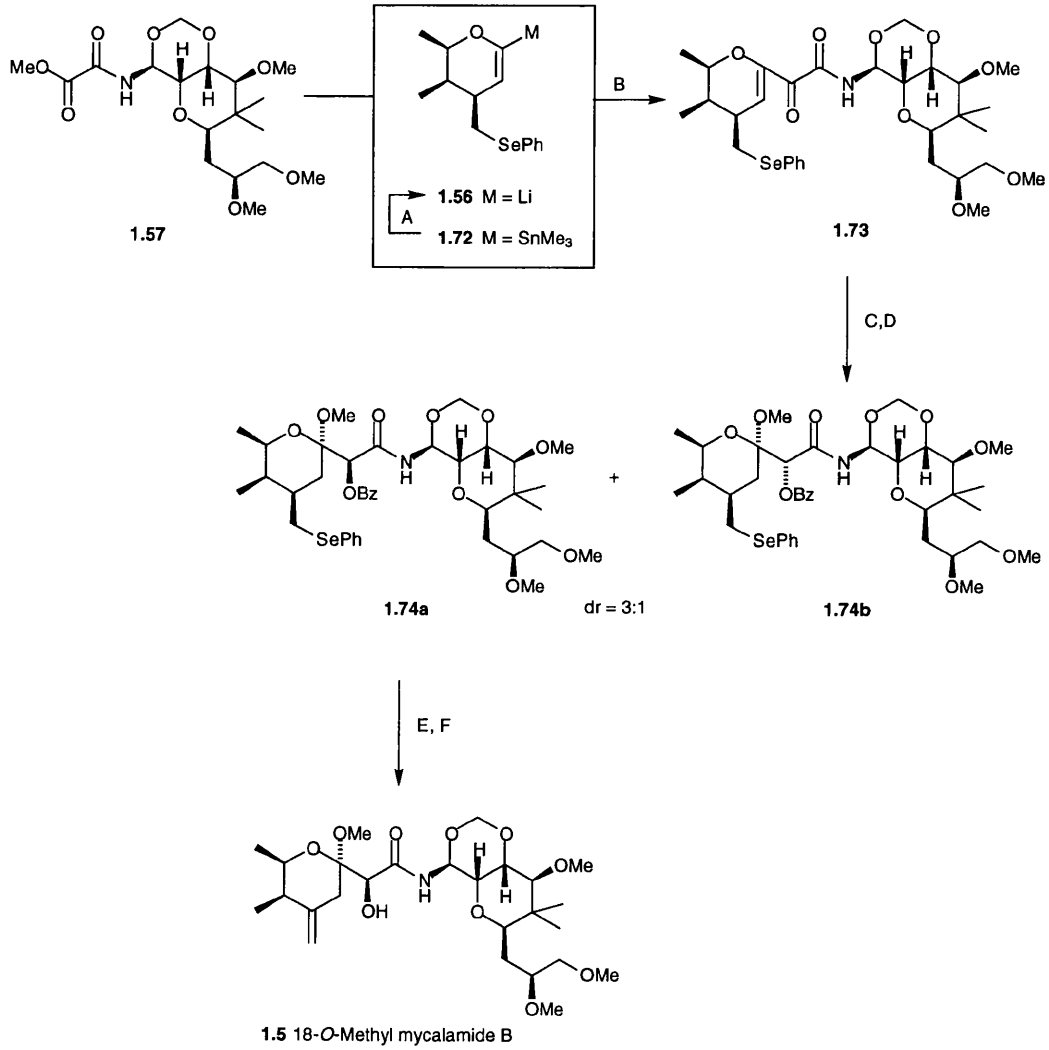
Scheme 1.19 *Reagents and conditions:*

A 95% a) PTSA, MeOH, Δ, 6 h; b) PivCl, pyr, CH_2Cl_2, rt, 4 h
B 70% MEMCl, Bu_4NI, DMAP, $(^iPr)_2NEt$, PhMe, 75-80°C, 15 h
C 98% LAH, Et_2O, 0°C, 25 min
D 90% Dess-Martin periodinane, CH_2Cl_2, rt, 1 h
E 70% $H_2C{=}CHCH_2OH$, PTSA, CH_2Cl_2, Δ, 22 h; then add $ZnCl_2$, Δ, 5 h
F 88% $(HCHO)_n$, $HCl_{(g)}$, CH_2Cl_2, rt, 85 min
G 71% $RhCl[PPh_3]_3$, DABCO, EtOH-H_2O, Δ, 1.75 h; $Hg(OAc)_2$, THF-H_2O
H 88% MsCl, DMAP, NEt_3, CH_2Cl_2; TASF, $TMSN_3$, CH_2Cl_2, −70→0,C, 8.5 h
I 77% H_2, 5% Pd-C, THF, rt; MeO_2C-COCl, DMAP, −20°C, 15 min

A series of five standard transformations converted benzylidene acetal **1.65** to its corresponding aldehyde **1.66** in 84% yield. Acid-catalysed acetalisation with allyl alcohol and removal of the MEM protecting group converted **1.66** to **1.67** which formed the required 1,3-dioxane ring upon treatment with paraformaldehyde and HCl gas. Removal of the allyl function in a single step proved problematic so a two step procedure was used. Isomerisation of the allyl ether **1.68** with Wilkinson's catalyst[61] and hydrolysis of the resultant enol ether

with the aid of mercuric acetate[62] gave the hemiacetals **1.69**. Conversion of **1.69** to the azides **1.70** followed by reduction to their aminals and *N*-acylation with methyl oxalyl chloride and DMAP returned the oxalamides **1.57** and **1.71** as a 2:1 diastereomeric mixture in favour of the unnatural stereochemistry at C-10.

To complete the synthesis of 18-*O*-methyl mycalamide B the left and right fragments (**1.56** and **1.57** respectively) were coupled together applying the metallated dihyropyran approach as developed during a synthesis of pederin[36] (scheme 1.20).



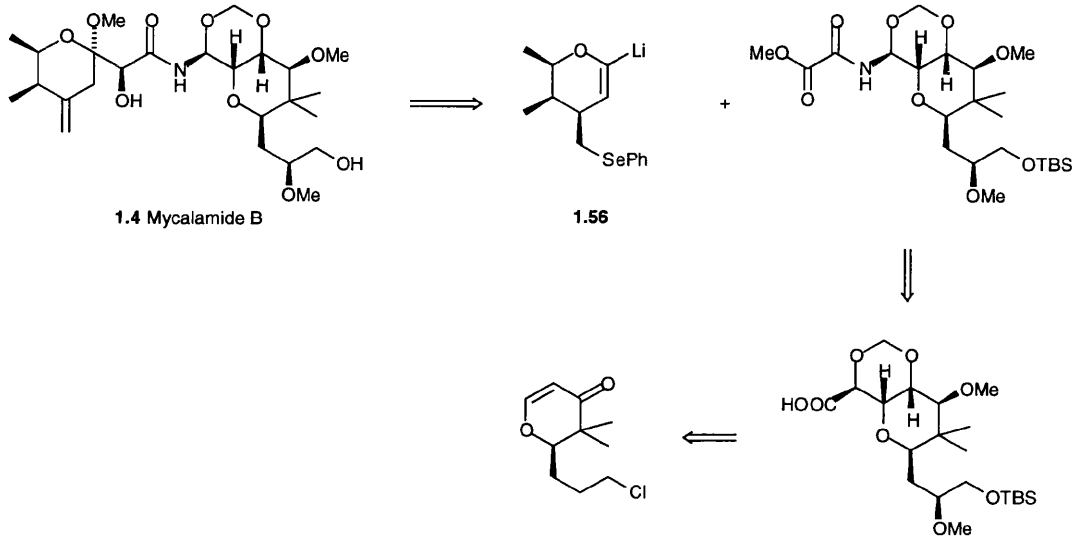
Scheme 1.20 *Reagents and conditions:*

A ↓ stannane **1.72** (3 eq), ^{n}BuLi, THF-hexanes, –78°C, 15 min
B 78% TMEDA, ester **1.57**, THF, –78°C, 2 h
C ↓ a) *s*-Bu_3BHLi, THF, –95°C, 15 min; b) CSA, MeOH–CH_2Cl_2, rt, 40 min
D 76% BzCl, DMAP, $(^{i}Pr)_2NEt$, CH_2Cl_2, rt
E 95% a) $NaIO_4$, MeOH-H_2O, rt, 20 min; b) NEt_3-PhH, Δ, 2 min
F 92% LiOH, MeOH, rt, 30 min

51.8 % overall yield (8 steps)

The lithiated dihydro-2*H*-pyran **1.56** in the presence of TMEDA coupled to the oxalamide **1.57** giving the acylated dihyropyran derivative **1.73** in 64% yield. Reduction of the keto function in **1.73** with LiBH(*s*-Bu)$_3$ at –95°C followed by the acid-catalysed addition of MeOH to the dihydropyran gave a pair of diastereoisomers which were separated after benzoylation. To install the *exo*-methylene function the phenyl selenide function was oxidised to a phenyl selenoxide and heated for 2 minutes causing elimination. The benzoate was removed by LiOH hydrolysis to give 18-*O*-methyl mycalamide B.

In 1998 we published a synthesis of mycalamide B **1.4** which exploited a Curtius rearrangement to install the C-10 stereogenic centre and the metallated dihydropyran approach to construct the acyl aminal bridge of mycalamide B **1.5** [22] (scheme 1.21). The publication summarises some of the work presented in this thesis.



Scheme 1.21

Chapter 2

Our Synthetic Approach to Theopederin D

2.1 Our Objectives

At the beginning of our study we set ourselves a list of objectives. They were:

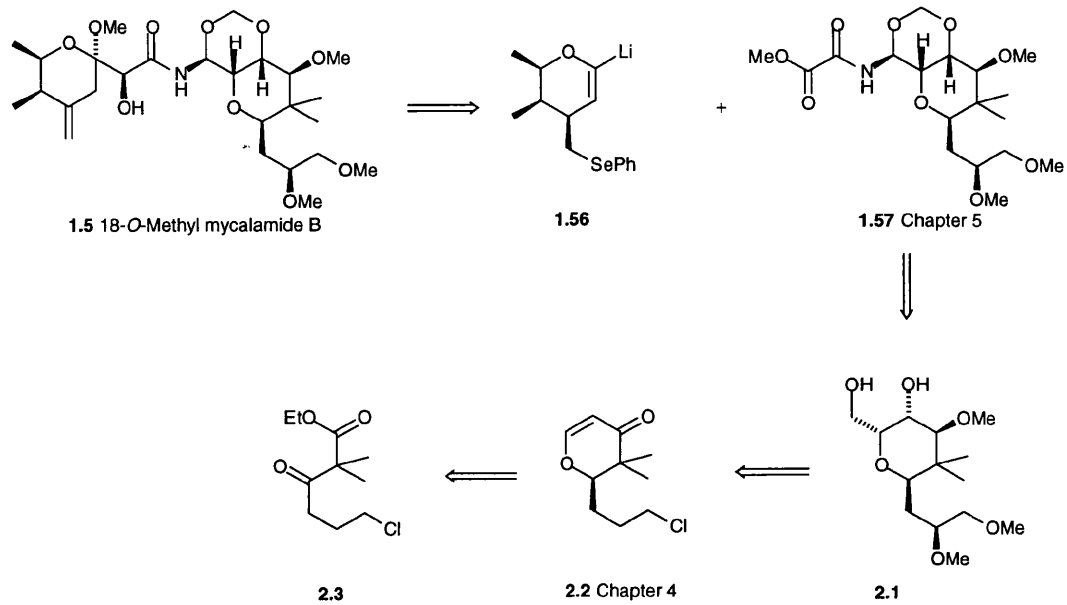
- To design a synthesis towards theopederin D (**1.1d**) which could also be adopted to synthesise mycalamide A and B (**1.3** and **1.4**), onnamide A (**1.2**) and pederin from advanced intermediates.
- To develop the technology to synthesise derivatives of the natural products for biological screening.
- To form the stereogenic centres with a high degree of stereoselectivity.
- To use readily available and cheap starting materials and reagents.
- To avoid column chromatography for the purification of large scale intermediates.

We believed success would depend on our ability to develop a route that could provide suitably large quantities of early intermediates quickly and cheaply. We also needed to build a degree of versatility into the early intermediates allowing us to synthesise the theopederins, mycalamides, pederin and analogues without returning to the beginning of the route for each target. The practical implications were that column chromatography should be avoided for the purification of large scale intermediates, thus early reactions in our sequence should provide products which can be purified by distillation, recrystallisation or be used crude in the next step. In order to develop an efficient beginning to our synthesis we chose 18-*O*-methyl mycalamide B **1.5** as our initial target. 18-*O*-Methyl mycalamide B had already been synthesised within the Kocienski group allowing us to build on previous experience.[17] Once the synthesis of 18-*O*-methyl mycalamide B was complete our aim was to evaluate the route and redirect our synthetic effort towards a synthesis of theopederin D.

2.2 Synthetic Strategy

Our approach towards 18-*O*-methyl mycalamide B was based upon that already published by Kocienski *et al* making use of the successful lithiated dihydropyran approach to construct the

acyl aminal bridge (chapter 1, scheme 1.20).[17] Our retrosynthetic analysis is shown in scheme 2.1.

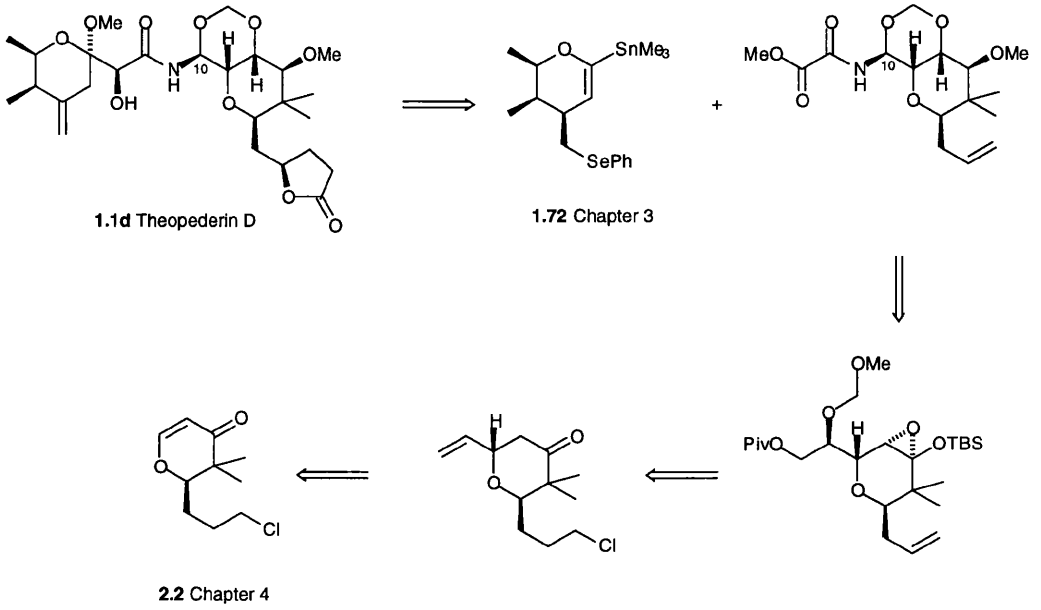


Scheme 2.1

The target molecule was divided into two fragments by breaking the C6-C7 bond giving rise to the known lithiated dihydropyran **1.56**[36] and the known oxalamide **1.57**.[17] We proposed to synthesise the oxalamide **1.57** from the known diol **2.1** using similar chemistry to that described during a previous synthesis of 18-*O*-methyl mycalamide B.[17] We examined the previous synthesis of diol **2.1** and concluded it was long (requiring a 3 step detour to insert the C-13 stereogenic centre), expensive (due to the high cost of chiral starting material [(*S*)-butan-1,2,4-triol]) and inflexible (the C15-side chain functionality was introduced at the start of the route preventing any versatility in the C15 side chain). Therefore we designed a new synthesis of diol **2.1** starting from β-keto ester **2.3** *via* enone **2.2**. The synthesis of enone **2.2** is discussed in chapter 4 and completion of the synthesis of 18-*O*-methyl mycalamide B *via* diol **2.1** is discussed in chapter 5. We also examined the previous synthesis of the lithiated dihydropyran **1.56** and concluded the route was also long and thus developed a shorter, highly diastereoselective route starting from ethyl (*S*)-lactate which is described in chapter 3.

Once the new synthesis of 18-*O*-methyl mycalamide B was complete, we evaluated the route to see how it could be adapted to the synthesis of theopederin D (**1.1d**). We concluded the synthesis of the enone **2.2** (scheme 2.1) met all of our objectives that we set ourselves at the beginning of our study; however, the route after **2.2** needed further improvement. Our new approach (scheme 2.2) once again included the lithiated dihydropyran approach to construct the acyl aminal bridge but in light of the work by Roush[25] and Hoffmann[18,20], using a Curtius rearrangement to install the C-10 stereogenic centre, we planned to install the C-10

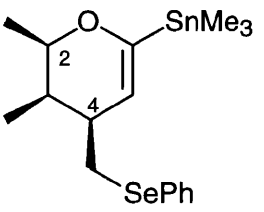
stereogenic centre *via* a Curtius rearrangement. We planned to leave the functionalisation of the C-15 side chain to the last stages of the synthesis incorporating a terminal olefin in the C-15 side chain as a "versatile synthetic handle". A retrosynthetic analysis of our approach towards theopederin D (**1.1d**) is shown in scheme 2.2 and our synthesis of theopederin D is described in chapter 6.



Scheme 2.2

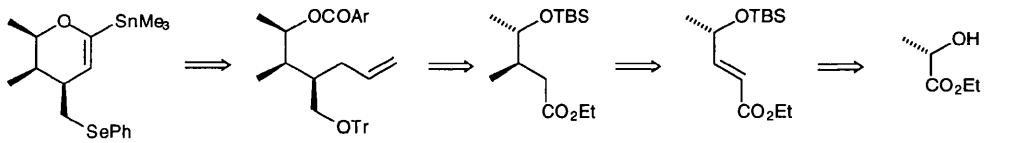
Chapter 3

Construction of the Left Fragment



1.72

Vinyl stannane **1.72** is an intermediate common to our synthesis of 18-*O*-methyl mycalamide B **1.3** and theopederin D **1.1d** and has been previously synthesised by Kocienski during a synthesis of pederin **1.5**.[36] The synthesis was considered to be too long and expensive and thus a more expedient synthesis was developed. Our approach was based upon two diastereoselective key steps: 1) 1,4-conjugate addition of a methyl cuprate to homochiral enoate **3.3** [63,64]and 2) diastereoselective allylation to the corresponding potassium enolate of β-methyl ester **3.2**. Ethyl (*S*)-lactate **3.4** was selected as the cheap chiral starting material (£1.60/mole). Our retrosynthetic analysis is shown in scheme 3.1.

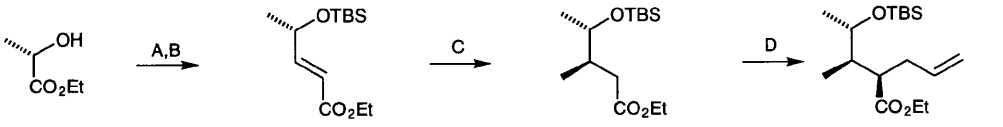


1.72 **3.1** Ar = *p*-ClC$_6$H$_4$ **3.2** **3.3** **3.4** Ethyl (*S*)-lactate

Scheme 3.1

3.1 The Synthesis of *p*-Chlorobenzoate 3.1

The synthesis of **3.5** from ethyl (*S*)-lactate **3.4** is shown in scheme 3.2.



3.4 **3.3** **3.2** (dr > 15:1) **3.5** (single diastereoisomer)

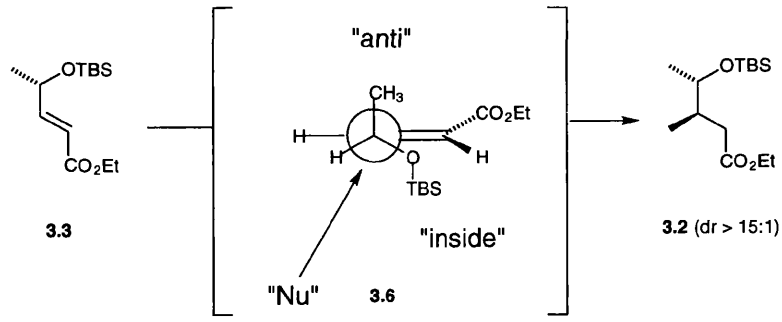
Scheme 3.2 *Reagents and conditions:*

A 99% TBSCl, Et_3N, DMAP, CH_2Cl_2, Δ, 24 h
B 77% a) DIBAL, CH_2Cl_2, –78°C, 30 min; b) Triethyl phosponoacetate, NaH, THF, rt, 40 min
C 75% Me_2CuLi, TMSCl, HMPA, THF–Et_2O, –95°C (3.75 h) → –50°C (1 h)
D 80% KHMDS (1 eq), allyl bromide (5 eq), THF, –78°C, 3.5 h

45.7% overall (5 steps)

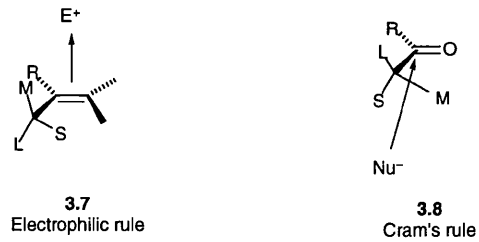
Ethyl (*S*)-lactate **3.4** was converted to the ester enoate **3.3** using standard procedures[65] in 75% yield over 3 steps on a 244 mmol scale (scheme 3.2). Diastereoselective 1,4-conjugate addition of Me_2CuLi to ester enoate **3.3** in the presence of TMSCl at –95°C gave the β-methyl ester **3.2** in a favourable 24:1 mixture of diastereoisomers[63,64] as determined by integration of ^{13}C NMR spectra signals [^{13}C NMR (90 MHz, CDCl3): δ = 71.6 (major) and 70.7 (minor) ppm]. The yield was 75% after short path distillation on a 95 mmol scale. Enolisation of β-methyl ester **3.2** using KHMDS and subsequent allylation afforded the corresponding ester **3.5** as a single diastereoisomer. The ester **3.5**, after purification by short path distillation, was obtained in 80% yield.

Yamamoto[64] proposed a model for the diastereoselectivity of 1,4-conjugate addition of organocopper reagents to γ-alkoxy α,β-unsaturated carbonyl derivatives to explain the *anti*-stereoselectivity observed during the formation of **3.2**. Yamamoto showed the OTBS group occupied the more sterically demanding "inside position" (^1H NMR spectroscopic studies provided experimental evidence for this observation) and the methyl group occupied a position anti to the approaching nucleophile, which corresponds to the Cieplak electronic model[66]. Yamamoto also proposed that a chelation mechanism was not involved. Thus *anti*-approach of the nucleophile towards the conformer **3.6** shown in scheme 3.3 furnished ester **3.2** in accordance with experimental evidence.



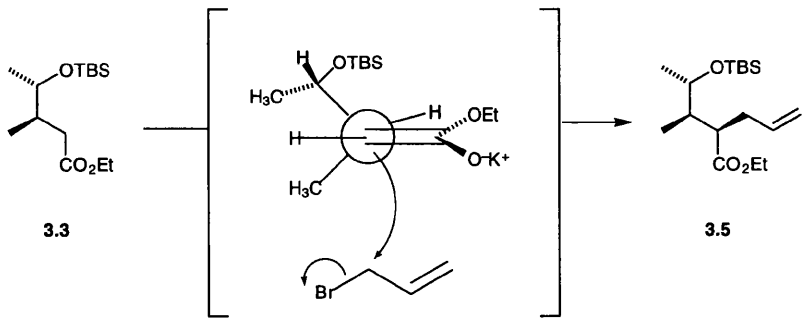
Scheme 3.3

To rationalise the high diastereoselectivity observed for the allylation of the potassium enolate derived from **3.2** to give **3.5** we must consider models describing electrophilic attack on trigonal carbon adjacent to a chiral centre. Houk proposed a rule for electrophilic attack in open chain-structures on trigonal carbon adjacent to a chiral centre, which is summarised in scheme 3.4, drawing **3.7**.[67] The argument states the preferred conformation has the "small" (S) substituent partly eclipsing the double bond and the electrophile approaching from within the double bond *anti* to the "large" (L) group. It follows that electrophilic attack should take place from the opposite side to that of the corresponding nucleophilic attack on a carbonyl group, and the electrophilic rule should prove to be the opposite of Cram's rule[68] which is summarised in drawing **3.8**, scheme 3.4



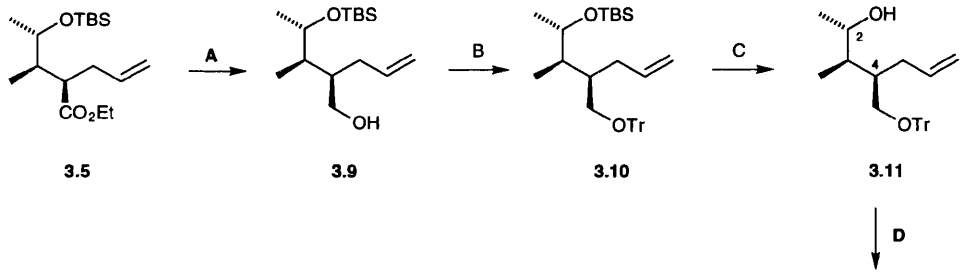
Scheme 3.4

Work by Fleming[69,70] and Yamamoto[71] on diastereoselectivity in the alkylation of enolates adjacent to a chiral centre has corroborated the "electrophilic rule" proposed by Houk[67] as does our work relating to the formation of **3.5**. The stereochemistry can be explained *via* the eclipsed model as shown in scheme 3.5 where allyl bromide approaches the double bond *anti* to the $C(CH_3)OTBS$ group to produce **3.5**. The result indicates the high level of diastereoselectivity can be attributed to the much greater steric bulkiness of the $C(CH_3)OTBS$ group over the CH_3 group.



Scheme 3.5

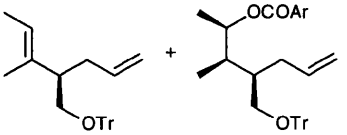
To continue the synthesis towards **3.1** (scheme 3.6), reduction of ester **3.5** to alcohol **3.9** proceeded cleanly using DIBAL in 89% yield after Kugelrohr distillation. Subsequent protection of the primary alcohol **3.9** as its trityl ether **3.10** occurred in 94% yield. The TBS function was removed effectively by refluxing in a solution of TBAF and THF to give alcohol **3.11** which was used crude in the next step. Using the Mitsunobu protocol[72] the C-2 stereogenic centre was inverted to form the *p*-chlorobenzoate ester **3.1** in 76% yield over two steps. The elimination product **3.12** (5%) was formed during the Mitsunobu inversion reaction but was easily removed by the first column chromatography of the synthesis.



Scheme 3.6 *Reagents and conditions:*

A 89% DIBAL (2.1 eq), CH_2Cl_2, 5°C, 1 h
B 94% TrCl, Et_3N, DMAP, CH_2Cl_2, rt, 12 h
C ↓ TBAF•$3H_2O$ (1.8 eq), THF, Δ, 5 h
D 76% *p*-$ClC_6H_4CO_2H$, DIAD, Ph_3P (1.75 eq each), THF, −10°C, 3 h

63.6% overall (4 steps)

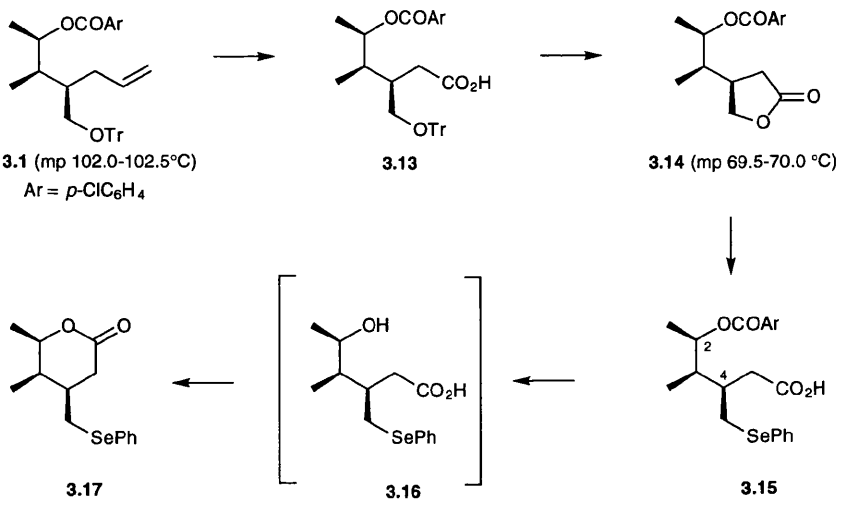


3.12 5%

3.1 (mp 102.0-102.5°C)
Ar = *p*-ClC_6H_4

3.2 Completion of the Left Fragment Synthesis

Completion of the synthesis of left fragment (**1.72**) synthesis is shown in scheme 3.7.



Scheme 3.7 *Reagents and conditions:*

A 53% $RuCl_3$ (6.6 mol%), $NaIO_4$ (4 eq), $MeCN–CCl_4–H_2O$, rt, 5 h
B 58% MeOH, PTSA (0.13 eq), rt, 24 h
C 88% Ph_2Se_2, $NaBH_4$, EtOH, Δ, 11 h
D ↓ $(^iBu)_2BuAlHLi$, THF, –20°C, 3 h
E 72% 2M $HCl_{(aq)}$, Et_2O, rt, 24 h
F 70% (a) KHMDS, HMPA, THF, –80°C; (b) $PhN(Tf)_2$
(b) Me_6Sn_2, $(Ph_3P)_4Pd$

13.6% overall (6 steps)

The terminal olefin of **3.1** was subjected to Sharpless oxidation conditions to return carboxylic acid **3.13** in 53% yield.[73] The trityl protecting group was removed with PTSA in MeOH to give a γ-hydroxy carboxylic acid which spontaneously cyclised to the γ-lactone **3.14**. We were fortunate to find that the γ-lactone **3.14** was a highly crystalline compound allowing us to remove all minor diastereoisomeric impurities in a single recrystallisation. Cleavage of the alkoxy bond in γ-lactone **3.14** by refluxing in an ethanol solution of sodium borohydride and diphenyl diselenide gave the required carboxylic acid **3.15** in 88% yield.[74] To form δ-lactone **3.17** the *p*-chlorobenzoate group had to be removed to leave the free alcohol **3.16**. Saponification using 2M $NaOH_{(aq)}$ hydrolysed the ester function cleanly; however, 5% epimerisation was observed at the C-2 centre by ^{13}C NMR spectroscopy. To avoid epimerisation at C-2 the ester **3.15** was converted to its corresponding alcohol **3.16** by reduction using an "ate complex"[75], formed by the equimolar combination of ^{n}BuLi and DIBAL. Acidic work-up gave the required δ-lactone **3.17** in 72% yield. Carboxylic acids are known to be inert towards the ^{n}BuLi-DIBAL "ate complex" which allowed us to selectively reduce the ester function in the presence of the carboxylic acid function in **3.15**. Conversion

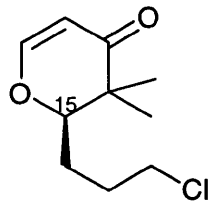
of **3.17** to vinyl stannane **1.72** proceeded in 70% yield using conditions previously developed by Kocienski *et al* [36].

3.3 Conclusion

Vinyl stannane **1.72** was synthesised in 15 steps in 12.7% overall yield starting from ethyl (*S*)-lactate. The above sequence is an improvement on the previously published route[36] with the improvements being made primarily at the beginning of the synthesis, employing a highly diastereoselective 1,4-conjugate addition of a methyl cuprate to enoate **3.3** and a highly diastereoselective allylation of the potassium enolate of **3.2**. Both transformations were high yielding and avoided the use of column chromatography for purification.

Chapter 4

Synthesis of Dihydropyranone



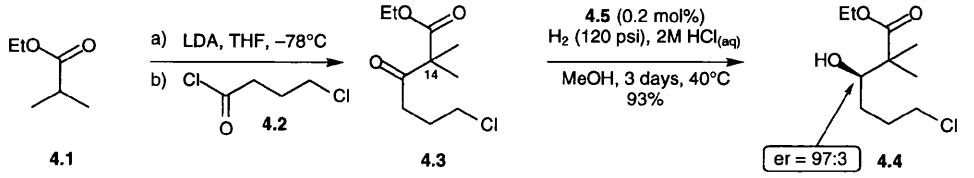
2.2

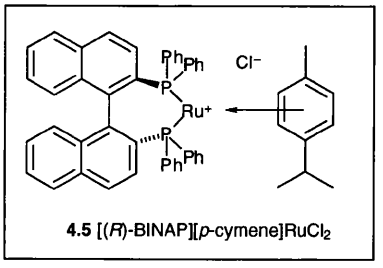
Dihyropyranone **2.2** is an intermediate common to our syntheses of 18-*O*-methyl mycalamide B **1.5**[17] and theopederin D **1.1d**.[1] It is also an intermediate which may be applied towards a synthesis of pederin **1.6**[6], onnamide A **1.2**[4], the mycalamides A **1.2** and B **1.3**[2,3] and the theopederins A-E **1.1a-e**[1]. In order to develop a synthesis that would produce all of these natural products, we aimed to prepare the dihydropyranone **2.2** on a large scale using cheap starting materials and reagents and avoiding column chromatography. Control of the C-15 stereogenic centre was identified as the most significant challenge.

4.1 Creation of the C-15 Stereogenic Centre

The C-15 stereogenic centre was created efficiently by two different routes. The first began by condensing the lithium enolate of ethyl isobutyrate **4.1** with 4-chlorobutanoyl chloride **4.2** to give β-keto ester **4.3** followed by catalytic asymmetric hydrogenation (scheme 4.1). Enantioselective reductions of β-keto esters have been reported using biological or biochemical transformations[76-78] and enantioselective catalytic hydrogenation[79-81]. We avoided biotransformation methods because they are highly substrate dependant often resulting in variable yields and poor enantioselectivity. In addition such methods can be impractical; for example, bakers' yeast reduces ethyl 3-oxobutanoate to ethyl (*S*)-3-hydroxybutanoate in 88-97% ee and 70-80% yield, but in order to obtain high (95-97%) ee, the substrate concentration should be kept below 1 g/L[82,83]. Enantioselective catalytic hydrogenation of β-keto esters is an alternative complementary methodology[79-83] allowing easy control of the chiral outcome, access to both antipodes with equal ease and a higher substrate concentration than the biological version is tolerated. In 1987 Noyori and co-workers[83] reported the use of catalytic $RuCl_2$[(*R*)-BINAP] in methanol in conjunction with $H_{2(g)}$ (1500 psi) to reduce β-keto esters with 99% ee in 99% yield after 46 hours. However, since the initial publication only two research groups reported the use of Noyori's procedure in a target-directed synthesis over a three year period[84-86]. The reason was probably due to the high pressure required and the difficulty in obtaining the air sensitive catalyst. In 1991,

Taber[80] reported the use of a $RuCl_2[(R)\text{-BINAP}]\bullet NEt_3$ catalyst that needed no purification and required a pressure of only 50 psi at 80°C to reduce β-keto esters with excellent ee. King and co-workers[81] then demonstrated that the addition of 1 mol% of 2M methanolic HCl to the reaction mixture as described by Taber accelerated the reduction allowing low pressure (40 psi) and low temperature (40°C) to be used and the reaction was complete after only 8 hours. Therefore, catalytic asymmetric hydrogenation of β-keto ester **4.3** (scheme 4.1) using 0.2 mol% of [(*R*)-(+)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl] chloro (*p*-cymene) ruthenium chloride **4.5**[87] (available from Aldrich) in methanol at 120 psi and 40°C for 3 days gave the required (*R*) configuration of the β-hydroxy ester **4.4** in 93% yield. The enantiomeric ratio was determined as 97:3 by integration of C14-Me singlets of the (*R*)-MTPA ester derivative from **4.4** [^{1}H NMR (270 MHz, C_6D_6): δ = 1.12 (major), 1.07 (minor) ppm]. A higher pressure of 120 psi and longer reaction time of 3 days was required to reduce **4.3** than that described by King[81]; this was due to the higher steric demand of the geminal-dimethyl group at C-14. To the best of our knowledge no other catalytic asymmetric reduction of a β-keto ester with a geminal-dimethyl group between the ketone and the ester has been reported in the literature.

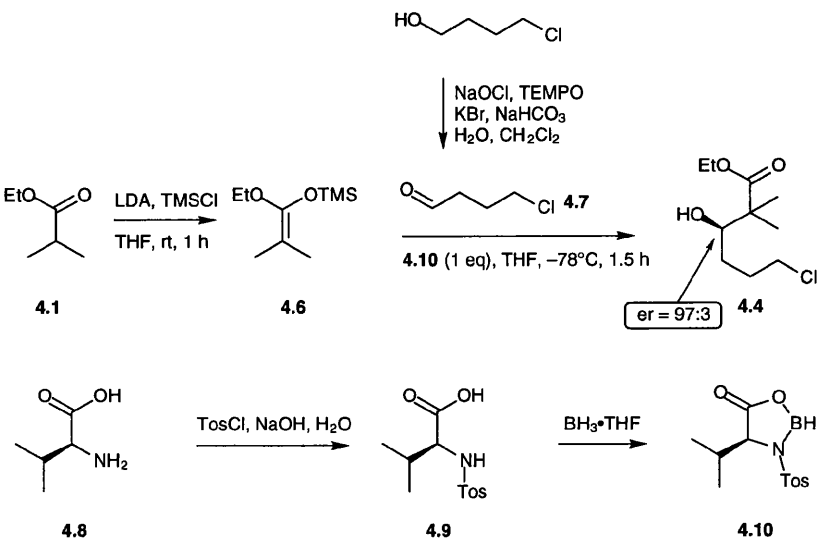




4.5 [(*R*)-BINAP][*p*-cymene]$RuCl_2$

Scheme 4.1

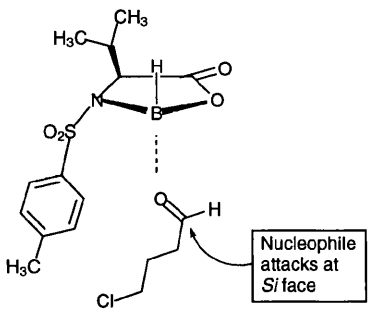
A second route to synthesise the same β-hydroxy ester **4.4** *via* a boron mediated asymmetric aldol reaction[84,85] was also developed and is shown in scheme 4.2.



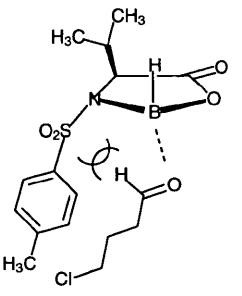
Scheme 4.2

Trimethylsilyl enol ether **4.6** and 4-chlorobutanal **4.7** were coupled mediated by homochiral borane **4.10**. The enantiomeric ratio was determined as 97:3 by integration of the C14-Me singlets of the (*R*)-MTPA ester derivative from **4.4**. Enantiomerically pure borane **4.10** was prepared in two steps from cheap L-valine **4.8** and the *N*-tosyl-L-valine **4.9** could be recycled from the asymmetric aldol reaction mixture in 98% yield. 4-Chlorobutanal **4.7** was prepared in 67-71% yield (450 mmol scale) by oxidation of 4-chlorobutanol using sodium hypochlorite and the free radical TEMPO under phase transfer conditions[86]. To obtain a good yield of 4-chlorobutanal **4.7** 1.2 equivalents of sodium hypochlorite were required.

A conformation of **4.10** is represented diagramatically in scheme 4.3 and is based on MM2 calculations performed by Kiyooka.[84] The isopropyl group governs the position of the sulfonamide group and together they define the co-ordination site for the aldehyde. The aldehyde co-ordinates with its *Si* face exposed to nucleophilic attack whilst co-ordination exposing the *Re* face of the aldehyde to nucleophilic attack is disfavoured due to steric repulsion.



Favoured conformation of aldehyde binding to boron



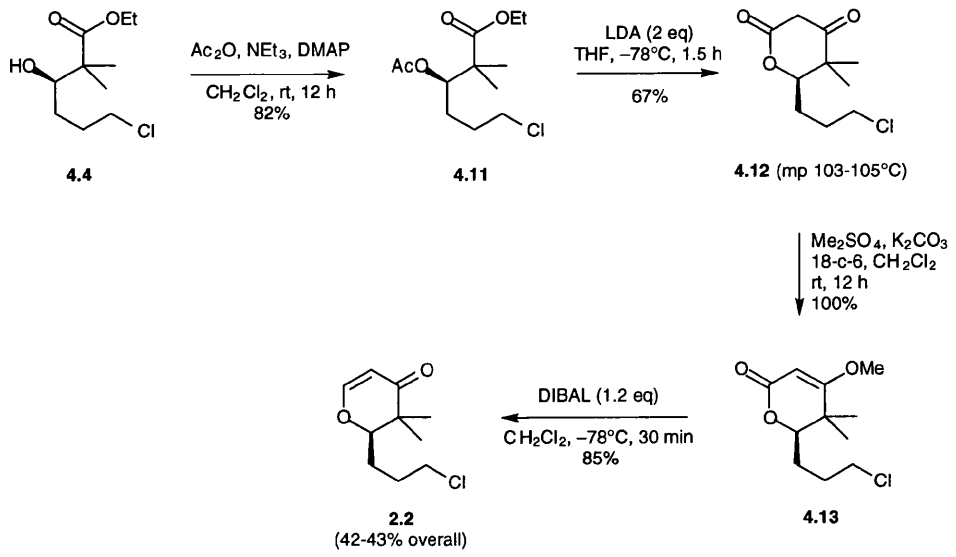
Disfavoured confirmation of aldehyde binding to boron

Scheme 4.3

To summarise, two separate reactions were developed to obtain chiral β-hydroxy ester **4.4**; an asymmetric aldol reaction (AAR) and a catalytic asymmetric hydrogenation (CAH). After a cost analysis of reagents and solvents the two procedures were found to be equally economical. The CAH however was a simpler reaction to perform in the laboratory requiring less reagent preparation. Unfortunately we were restricted to a 200 mL high pressure hydrogenator vessel allowing only 50 mmol batches of **4.4** to be prepared; therefore, we prepared the majority of β-hydroxy ester **4.4** using the AAR in 150 mmol batches using 3 litre glassware. There is an example in the literature where a similar CAH was performed on a 1 Kg scale[81] so we are confident in the suitability of the CAH reaction to be adopted for large scale preparation of **4.4**.

4.2 Conversion of β-Hydroxy Ester (4.4) to Dihydropyranone (2.2)

Conversion of β-hydroxy ester **4.4** to dihydropyranone **2.2** is shown in scheme 4.4.



Scheme 4.4

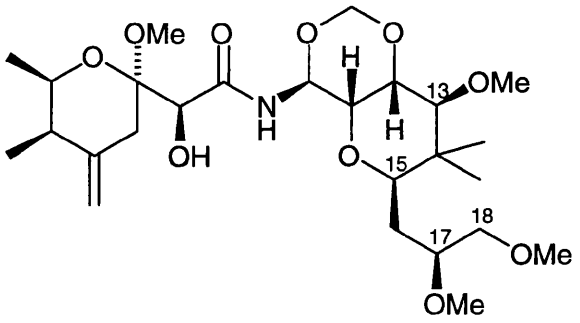
The crude β-hydroxy ester **4.4** from the asymmetric aldol reaction was converted to its corresponding acetate **4.11** using standard conditions in 74% yield over two steps and the pure β-hydroxy ester **4.4** from the asymmetric hydrogenation reaction was converted to the same acetate **4.11** using the same conditions in 82% yield over two steps (scheme 4.4). The acetate **4.11** was purified by short path distillation. Ring closure by Dieckmann condensation[88] of the acetate **4.11** using two equivalents of LDA gave the highly crystalline β-keto lactone **4.12**. β-Keto lactone **4.12** was purified to optical purity by three successive crystallisations (enantiomeric purity was determined by chiral HPLC after a further two steps). Five hundred grams (2.28 moles) of β-keto lactone **4.12** was prepared and we were able to store it indefinitely at room temperature. Enol ether **4.13** was formed by *O*-methylation of β-keto lactone **4.12** under phase transfer conditions, prior to reductive elimination with DIBAL to give the desired dihyropyranone **2.2** in 85% yield over two steps.

4.3 Conclusion

Optically pure dihyropyranone **2.2** was synthesised without the use of column chromatography in 42-43% yield over 5 steps from cheap starting materials. The dihyropyranone **2.2** formed a solid foundation on which to design syntheses of 18-*O*-methyl mycalamide B **1.5** and theopederin D **1.1d** (chapters 5 and 6).

Chapter 5

Synthesis of 18-*O*-Methyl Mycalamide B

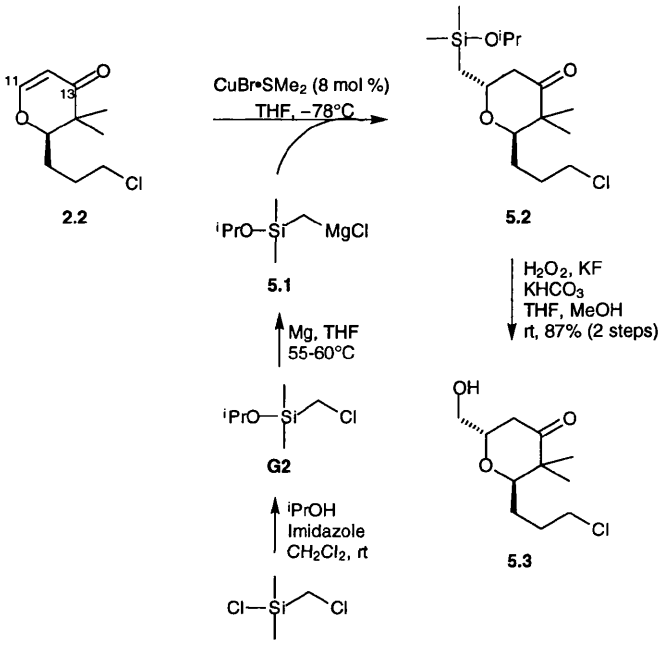


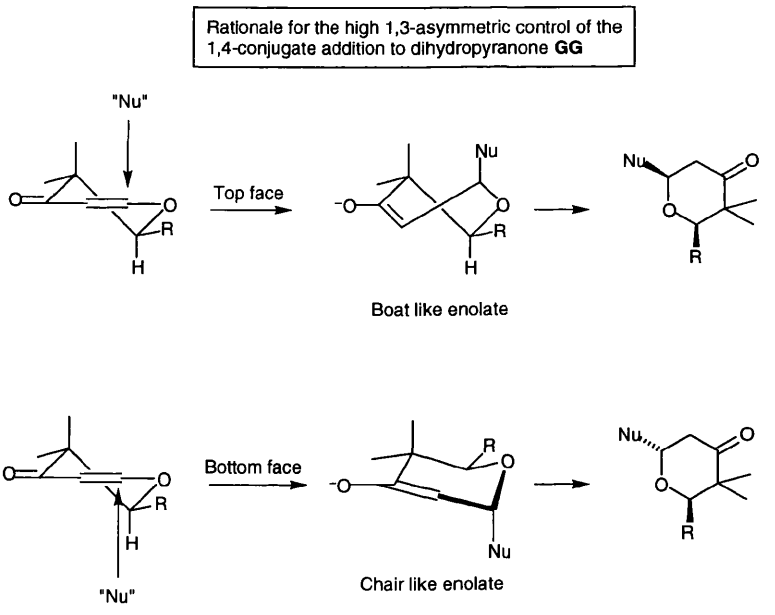
18-*O*-Methyl mycalamide B **1.5** has previously been synthesised by Kocienski *et al* using a metallated dihydropyran approach to couple the two fragments.[17] The route introduced the C-17 and C-18 methoxy functionalities at the beginning of the synthesis therefore excluding the possibility of further elaboration to any other targets, particularly the theopederins. The route was also long including a three step detour to provide the correct stereochemistry at C-13 (chapter 1, scheme 18). The inefficiency at the beginning of the synthesis, the lack of versatility and the poor stereocontrol at C-13 caused us to develop a new synthesis that was more efficient, diastereoselective and more versatile, especially with regard to the C-15 side chain functionality. The keys steps are: (a) diastereoselective conjugate addition of a hydroxymethyl anion equivalent **5.1** to dihyropyranone **2.2**; (b) oxidation of silyl enol ether **5.5** using dimethyl dioxirane; (c) diastereoselective Luche reduction[38] of ketone **5.8** and (d) the metallated dihyropyran approach to couple the two fragments.[17,36]

5.1 Introduction of the Stereogenic Centre at C-11

To introduce the single carbon at C-11 we chose isopropoxymethyldimethylsilane Grignard **5.1** as a hydroxymethyl anion equivalent. The addition of (isopropoxydimethylsilyl)methylmagnesium chloride **5.1** to aldehydes and ketones is described in the literature.[89] Attempts to add **5.1** to α,β-enones in the presence of a range of copper catalysts was also described in the literature; however, the addition occurred only to 2-cyclohexenone.[90] It is significant, therefore, that we were able to add Grignard reagent **5.1** to enone **2.2** (scheme 5.1). The Grignard reagent **5.1** underwent 1,4-addition to dihydropyranone **2.2** in the presence of $CuBr{\bullet}SMe_2$ with very high 1,3-asymmetric induction (the other diastereoisomer was not detected by ^1H NMR spectroscopy). A rationale for the high 1,3-asymmetric induction is as follows; attack of the nucleophile *syn* to the C-15 side chain (top face) would create a boat-like enolate whereas attack of the nucleophile *anti* to the

C-15 side chain (bottom face) creates a chair-like enolate which is of lower energy, thus accounting for the high diastereocontrol (scheme 5.1). A tentative stereochemical assignment of (11*S*,15*R*) was made based on a similar conjugate addition to a similar dihydropyranone used in a synthesis of pederin[36]. Confirmation of our assignment was made later on during our synthesis (*vide infra*). The isopropoxydimethylsilyl function was then converted to alcohol **5.3** using the Fleming-Tamao oxidation protocol[91-93] giving **5.3** in 87% yield after 2 steps.

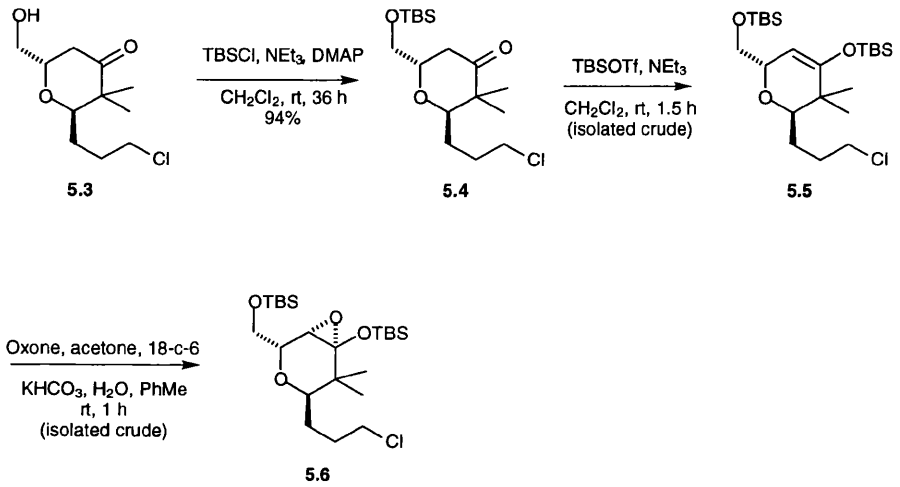




Scheme 5.1

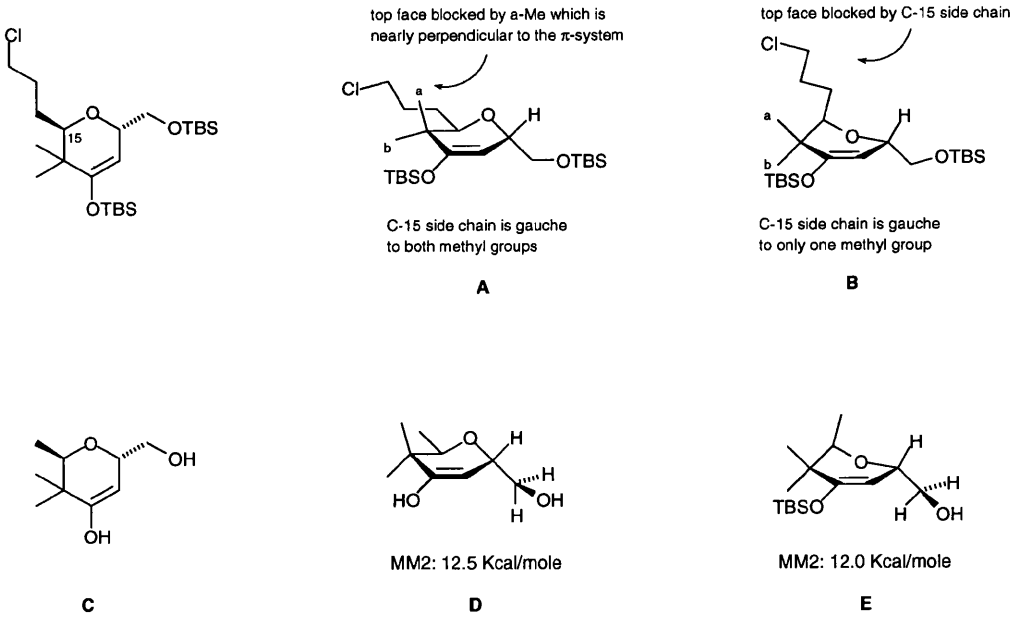
5.2 Introduction of the Stereogenic Centre at C-12

The alcohol **5.3** was converted to enol silane **5.5** in two standard transformations shown in scheme 5.2. To epoxidise enol silane **5.5** we chose the same epoxidation conditions as Kocienski *et al* used to epoxidise a similar enol silane **1.59** (chapter 1, scheme 18) during a synthesis of 18-*O*-methyl mycalamide B **1.5**.[17] Dimethyl dioxirane was generated *in situ* [58,59] under phase transfer conditions[60] converting enol silane **5.5** to the oxirane **5.6**. Attack from the apparently more hindered face of the double bond generated the oxirane **5.6** as a single diastereoisomer as determined by its ^{1}H and ^{13}C NMR spectra, however assignment of the oxirane stereochemistry was defined after the next step (*vide infra*).



Scheme 5.2

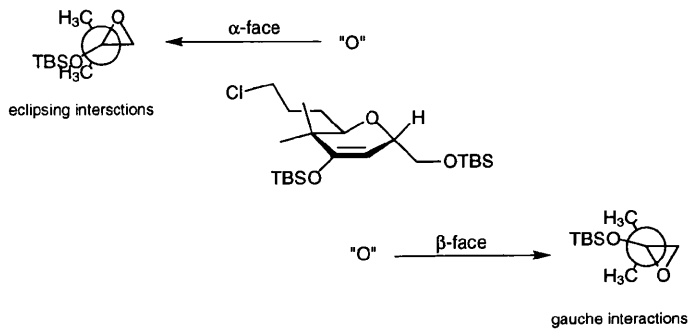
A rationale for the stereochemical outcome of the epoxidation of enol silane **5.5** is not obvious, for the epoxidation appears to be directed towards the more hindered face of the double bond *i.e. syn* to the CH_2OTBS group at C-11. Consider the two half-chair conformers **A** and **B**, scheme 5.3.



Scheme 5.3

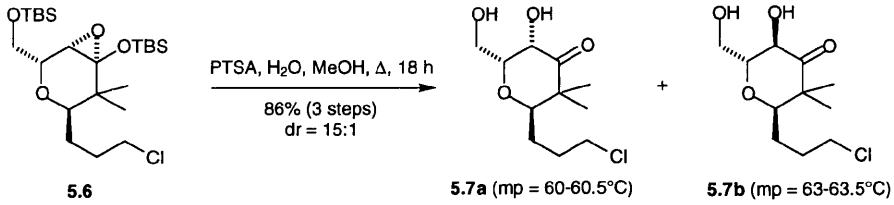
In the case of conformer **A**, the b-methyl and the CH_2OTBS groups are splayed outwards while the a-methyl is nearly perpendicular to the π-system thereby possibly offering greater steric impediment to attack from the α-face. The steric impediment to attack on the α-face is rather more pronounced in the half-chair conformer **B** wherein the C-15 substituent occupies an axial position in a 1,3 relationship to the alkene. Indeed, conformer **B** may be the preferred conformer since the C-15 side chain enters into only one gauche interaction with the a-methyl whereas in conformer **A**, the C-15 side chain is engaged in gauche interactions with both methyls. In order to gain some insight into the relative energies of conformers **A** and **B**, an MM2 calculation was performed on the model compound **C**. The half-chair conformers **D** and **E** (scheme 5.4 and appendix B) were identified as energy minima with conformer **E** being nearly 0.5 Kcal/mole more stable than conformer **D**. Thus steric arguments alone could account for the facial selectivity of epoxidation—especially if the reaction takes place preferentially through conformer **B**.

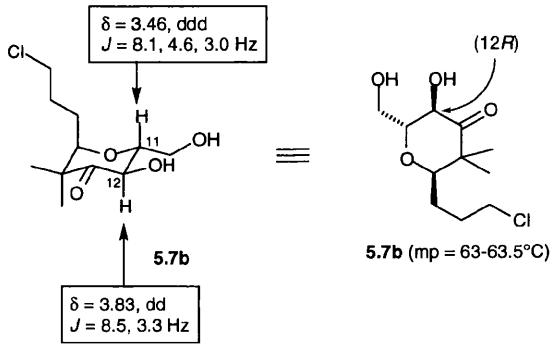
In the more ambiguous case of conformer **A**, facial selectivity might be rationalised by torsional effects[94] since epoxidation on the α-face leads to an eclipsing interaction between the OTBS group and the b-methyl whereas epoxidation on the β-face leads to a more favourable gauche interaction (scheme 5.4). However, the same analysis based on conformer **B** would predict that epoxidation on the α-face would be preferred. In the absence of any further information, we prefer the explanation based on steric effects.



Scheme 5.4

The oxirane **5.6** was then converted to the crystalline diols **5.7a** and **b** as shown in scheme 5.5.





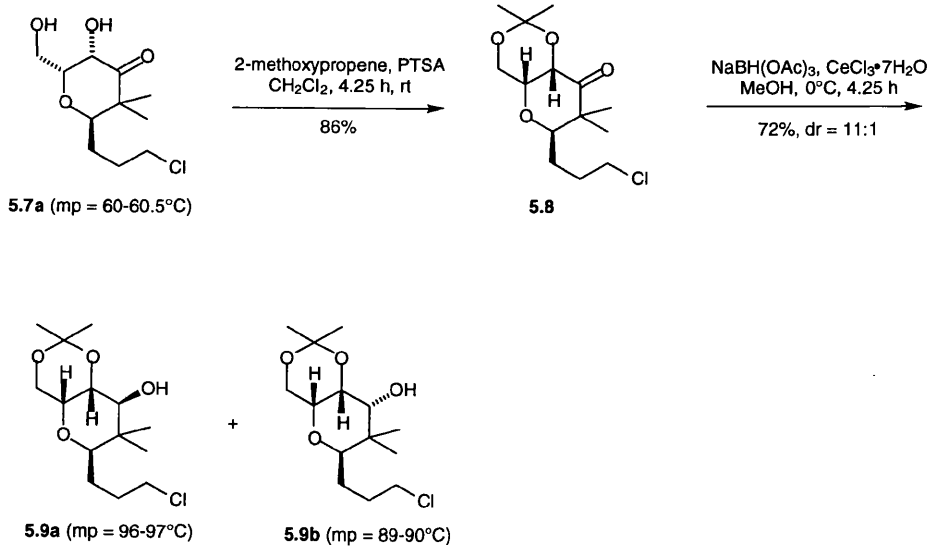
Scheme 5.5

Initially treatment of **5.6** with 40% HF and acetonitrile gave the alcohols **5.7a,b** as a 13:1 mixture of diastereoisomers but in variable yield (40-77%). However, refluxing the oxirane **5.6** in aqueous methanol and pyridinium *p*-toluenesulfonate gave the alcohols **5.7a,b** as a 15:1 mixture of diastereoisomers in 86% yield. The diastereoisomers **5.7a** and **5.7b** were separated by crystallisation to give optically pure diol **5.7a** followed by column chromatography of the mother liquor to give undesired diol **5.7b** and additional diol **5.7a**. The second method was the method of choice as the yields were consistently higher. The diastereomeric ratio at C-12 was determined by integration of doublets derived from the methine proton adjacent to the carbonyl [^{1}H NMR (270 MHz, C_6D_6): δ = 4.34 (minor) and 4.29 (major)]. The conformation of the minor isomer **5.7b** was determined as displaying an

axial-axial relationship between the C-11 and C-12 protons by examination of the vicinal coupling constants between C11-H and C12-H in its ^{1}H NMR spectra [^{1}H NMR (360 MHz, $CDCl_3$): δ = 3.83 (1H, dd, J = 8.5, 3.3 Hz, C12-H), 3.46 (1H, ddd, J = 8.1, 4.6, 3.0 Hz, C11-H) ppm]. The C12 stereogenic centre of **5.7b** was therefore tentatively assigned as (12*R*) and the corresponding centre of **5.7a** was then assigned as (12*S*) (scheme 5.5).

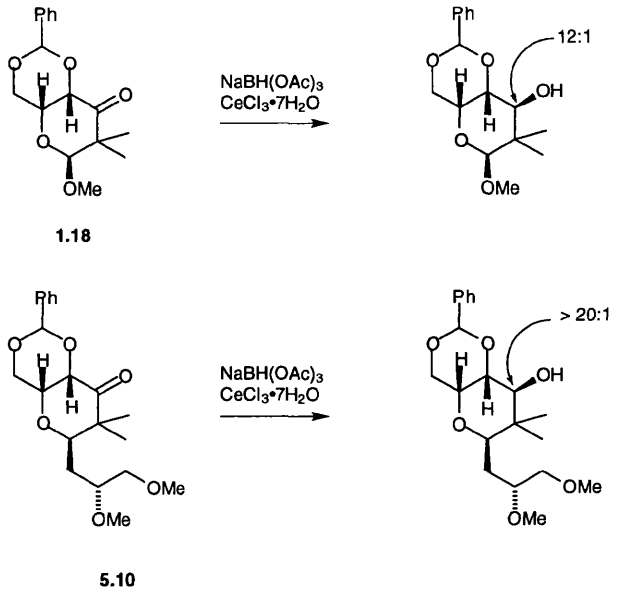
5.3 Introduction of the Stereogenic Centre at C-13

Before the introduction of the C-13 stereogenic centre, diol **5.7a** was protected as its isopropylidene acetal **5.8** in 86% yield using 2-methoxypropene and pyridinium *p*-toluenesulfonate (scheme 5.6). The ketone **5.8** was then reduced using modified Luche conditions[38] [($NaBH(OAc)_3$, $CeCl_3 \cdot 7H_2O$, MeOH, 0°C] to give the alcohols **5.9a** and **5.9b** in 72% yield. The diastereomeric ratio was determined as 11:1 at C-13 by the integration of singlets derived from C14-Me singlets in the ^{1}H NMR spectrum of **5.9a,b** [^{1}H NMR (270 MHz, C_6D_6): δ = 0.88 (minor) and 0.78 (major)].



Scheme 5.6

An explanation for the high level of diastereoselectivity observed during an analogous reduction of ketone **1.18** has been offered by Hong and Kishi during a synthesis of onnamide A **1.2**[29,95] and the same explanation was also offered by Kocienski and Davies for the same conditions to reduce a similar ketone **5.10** during a synthesis of 18-*O*-methyl mycalamide B**1.5**[17,96] (scheme 5.7).

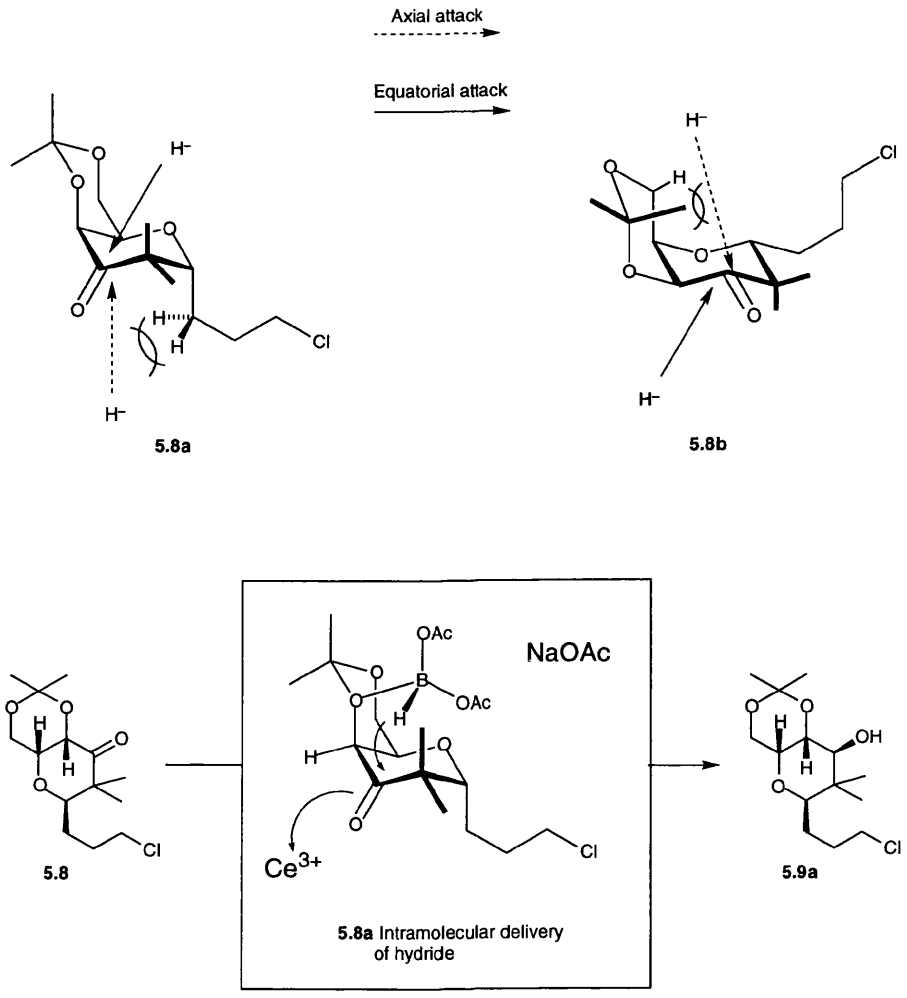


1.18

5.10

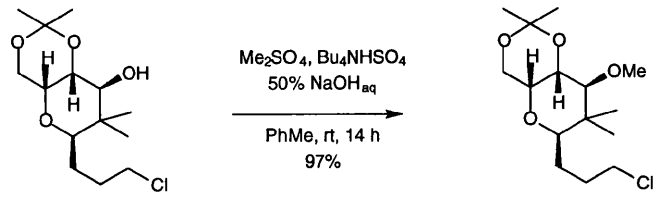
Scheme 5.7

It is accepted that the stereochemistry of nucleophilic addition to the carbonyl in cyclohexanones is controlled by a stereoelectronic factor stabilising the axial line of attack and steric factors opposing the axial line of attack as described by Cieplak.[66] We suggest (as did Kishi and Kocienski for their systems) that for ketone **5.8** the axial line of attack in both conformers **5.8a** and **5.8b** (scheme 5.8) is hindered leaving only the equatorial line of attack. Thus we propose that the reduction proceeds *via* an equatorial intramolecular hydride delivery in which the boron bonds to the axially oriented α-alkoxy group of **5.8a** in which the Ce^{3+} assists in the substitution of an acetate group on the boron. Experimental evidence supports the involvement of Ce^{3+} to activate the $NaBH(OAc)_3$ for in its absence no reduction is observed. The equatorial intramolecular delivery of a hydride as described above could only occur in conformer **5.8a** and not in conformer **5.8b** therefore explaining the high selectivity observed during the reduction of ketone **5.8**.



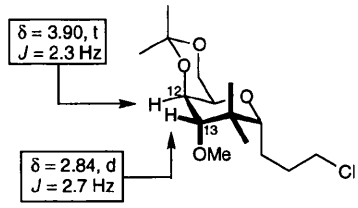
Scheme 5.8

Alcohol **5.9a** was then subjected to phase transfer *O*-methylation conditions to give **5.11** in excellent yield (scheme 5.9). ^{1}H NMR spectroscopic analysis of **5.11** revealed a small vicinal coupling constant between C12-H and C13-H therefore allowing us to conclude the 3D conformation of **5.11** is as shown in scheme 5.9 with C12-H and C13-H adopting a *trans*-diequatorial relationship [^{1}H NMR (270 MHz, $CDCl_3$): δ = 3.90 (1H, t, J = 2.3 Hz, C12-H) and 2.84 (1H, d, J = 2.7 Hz, C13-H) ppm].



5.9a (mp = 96-97°C)

5.11

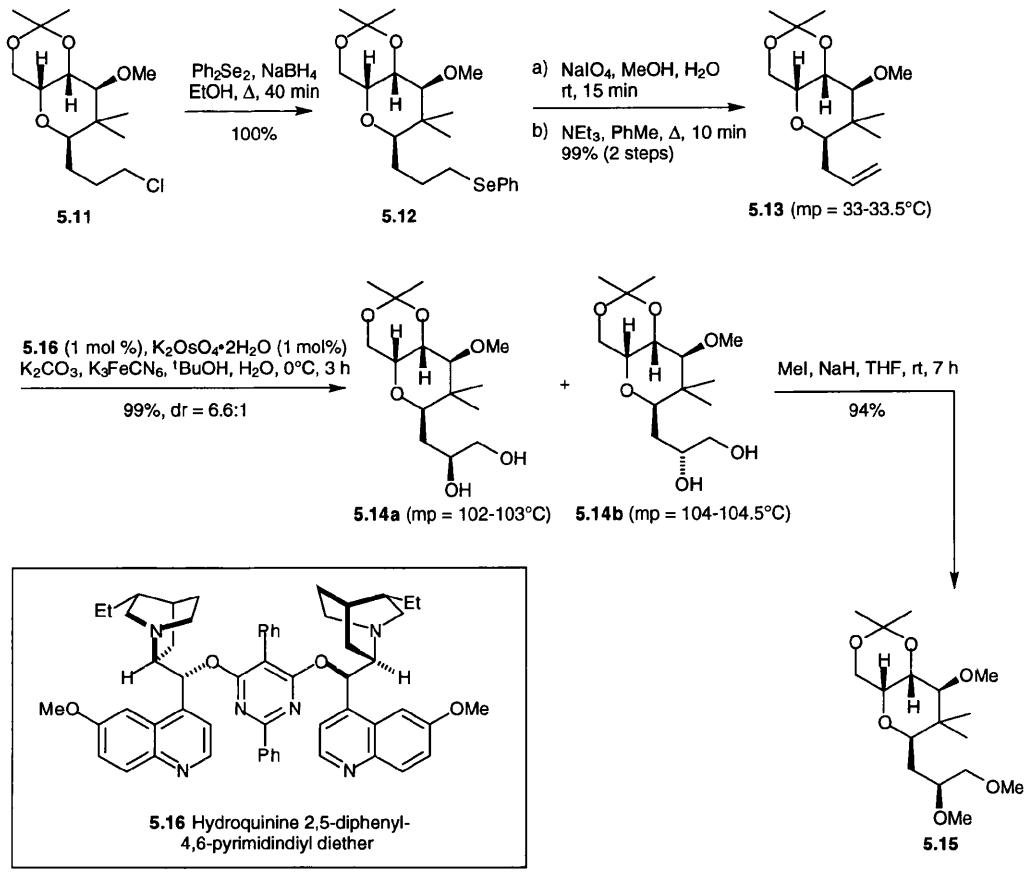


5.11 Conformational analysis

Scheme 5.9

5.4 Functionalisation of C-15 Side Chain

Having created the three contiguous stereogenic centres at C-11, C-12 and C-13 we turned our attention to the C-15 side chain and the creation of the C-17 stereogenic centre. The route is outlined in scheme 5.10.

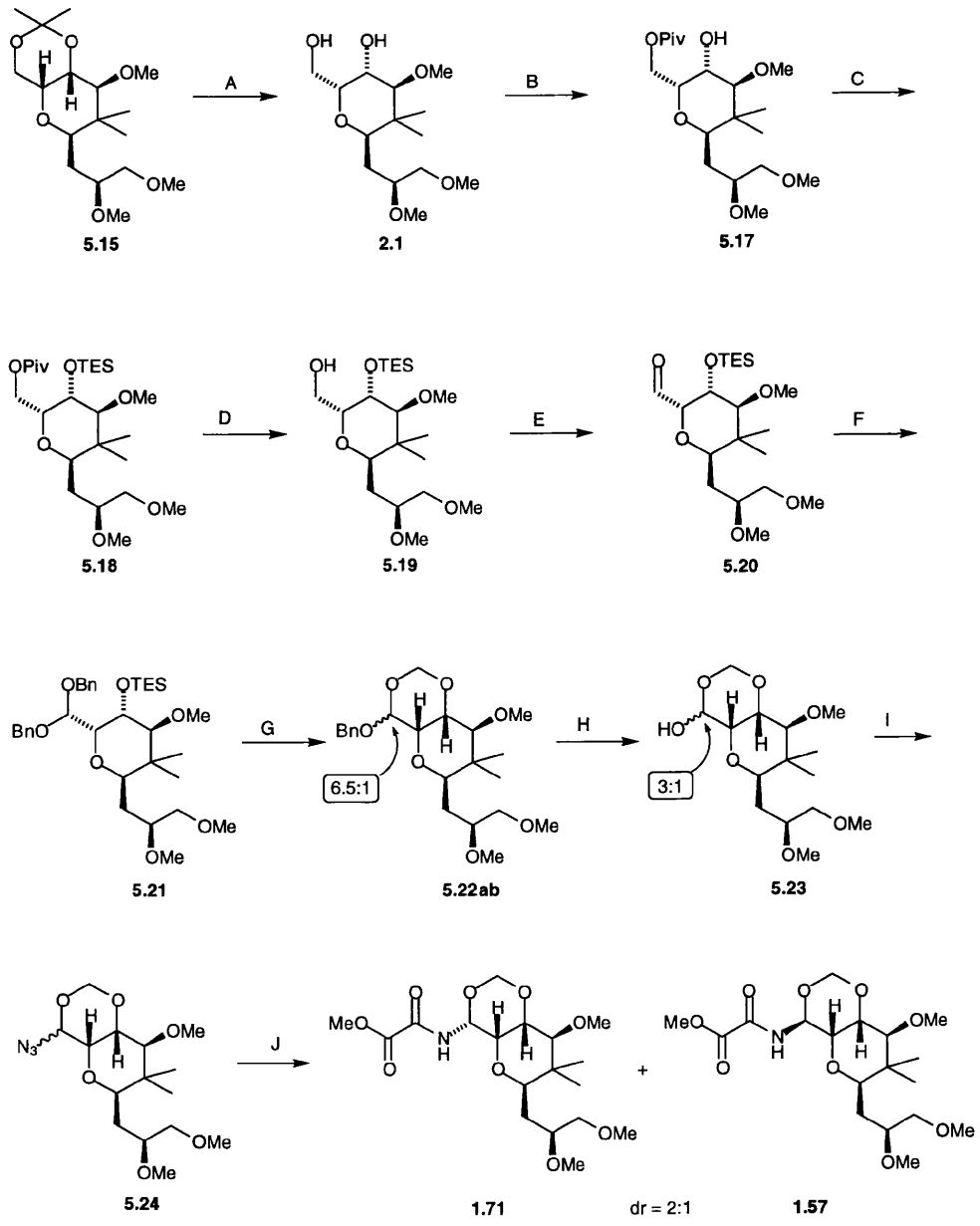


Scheme 5.10

Attempts to introduce unsaturation at C17-C18 by elimination of chloride using base, or conversion of the chloride to its corresponding iodide followed by base catalysed elimination resulted in complex mixtures. A high yielding solution was to convert the chloride **5.11** to its selenide **5.12** (diphenylselenide, $NaBH_4$, Δ, 100%), oxidise to the selenoxide ($NaIO_4$, MeOH, H_2O) and then heated at reflux for 10 min in a 1:1 mixture of toluene and triethylamine to eliminate selenoxide. Although three steps were involved they were quick and easy to perform returning the olefin **5.13** in 99% overall yield. Sharpless asymmetric dihyroxylation using hydroquinine 2,5-diphenyl-4,6-pyrimidindiyl diether **5.16** as ligand[97] converted olefin **5.13** to the diols **5.14a** and **5.14b** in 99% yield. The diastereomeric ratio was determined by ^1H NMR spectroscopy as 6.6:1 at C-17 by the integration of singlets derived from C14-Me [^1H NMR (270 MHz, C_6D_6): δ = 0.92 (minor) and 0.86 (major)]. The stereochemistry at the C-17 centre of **5.14a** was tentatively assigned as (17*S*) by comparison of the C-18 signals of the ^{13}C NMR spectra with their respective signals in the ^{13}C NMR spectra reported for mycalamide A [^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 66.5 ppm C-18 mycalamide A; δ = 66.0 ppm C-18 **5.14a**; δ = 67.7 ppm C-18 **5.14b**). Confirmation of the assignment was determined after a further two steps. Bis-*O*-methylation of diol **5.14a** (scheme 5.10) gave the required functionality in the C-15 side chain for 18-*O*-methyl mycalamide B **1.5**.

5.5 Completion of Our Synthesis of 18-*O*-Methyl Mycalamide B (1.5)

Our strategy to construct the 2,4,7-trioxabicyclo[4.4.0]decane ring and complete our synthesis of 18-*O*-methyl mycalamide B was the same as that developed by Kocienski *et al* during a previous synthesis of 18-*O*-methyl mycalamide B, however our choice of protecting groups and reagents was altered to improve yields and efficiency.[17] Our synthetic route is summarised in scheme 5.11.



Scheme 5.11 *Reagents and conditions:*

A ↓ PTSA, MeOH, rt, 45 min
B 99% PivCl, Pyr, CH_2Cl_2, rt, 4 h
C 99% TESCl, imidazole, DMF, rt, 2 h
D 98% DIBAL, CH_2Cl_2, –78°C, 30 min
E ↓ Dess-Martin periodinane, CH_2Cl_2, rt, 40 min
F 90% a) $(BnO)_3CH$, CSA, CH_2Cl_2, rt, 5 h; b) TBAF, THF, rt, 11 h
G 93% $(HCHO)_n$, $HCl_{(g)}$, CH_2Cl_2, rt, 1.5 h
H 87% H_2, 5% Pd/C, EtOAc, rt, 17 h
I 74% MsCl, DMAP, NEt_3, CH_2Cl_2; TASF, $TMSN_3$, CH_2Cl_2, –70→0°C, 8.5 h
J 57% H_2, 5% Pd/C, THF, rt; MeO_2C–COCl, DMAP, –20°C, 15 min

29.5% overall (13 steps)

1.5 18-*O*-Methyl mycalamide B

The isopropylidene acetal **5.15** was hydrolysed to form the known diol **2.1**[17] which allowed a comparison of analytical data; we were pleased to find our ^1H and ^{13}C NMR spectroscopic data for diol **2.1** were identical to that reported in the literature[17], thereby confirming all our

previous stereochemical assignments. A standard sequence of protection and deprotection steps followed, returning the primary alcohol **5.19**. Dess-Martin periodinane oxidation[98] of **5.19** furnished the unstable aldehyde **5.20** which was used immediately in the next step. Swern oxidation[41] was unsuitable because traces of sulphur poisoned the palladium catalyst used later on during the synthesis. A two step, one pot procedure converted aldehyde **5.20** to dibenzyl acetal **5.21** using tribenzyl orthoformate[99] and camphorsulphonic acid followed by the addition of TBAF. Triallyl orthoformate was used during a previous synthesis of 18-*O*-methyl mycalamide B but the allyl acetal proved problematic to remove,[17] whereas the benzyl group was easy to remove. The 1,3-dioxane ring was installed by treatment of **5.21** with paraformaldehyde in the presence of $HCl_{(g)}$ to give the benzyl acetals **5.22a,b** in 93% yield (dr = 6.5:1, separated by column chromatography for characterisation). Hydrogenation of the 6.5:1 diastereomeric mixture of benzyl acetals **5.22a,b** returned the hemi-acetals **5.23** in 87% yield as a 3:1 mixture of diastereoisomers. It was at this point that our synthesis converged with a previous synthesis of 18-*O*-methyl mycalamide B.[17] Hemi-acetals **5.21** were converted to azides **5.24** which were reduced to a sensitive mixture of aminals and immediately acylated with methyl oxalyl chloride in the presence of DMAP. A 1:2 mixture of diastereoisomers **1.57** and **1.71** were obtained in favour of the unnatural stereochemistry at C-10 in 57% yield over 2 steps. The oxalamides **1.57** and **1.71** were separated by column chromatography and their ^{1}H and ^{13}C NMR spectra were identical to those reported in the literature.[17] The oxalamide **1.57** was converted to 18-*O*-methyl mycalamide B **1.5** in seven steps, as described in the literature[17] .

5.6 Conclusion

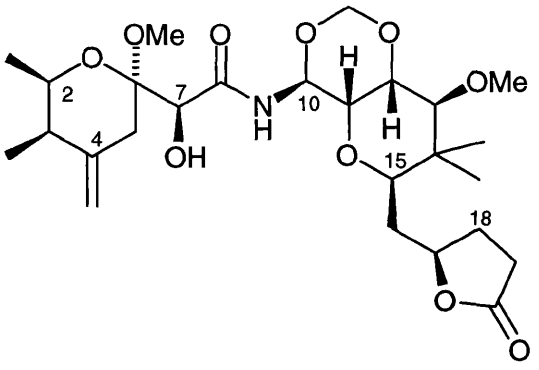
On completing the synthesis of 18-*O*-methyl mycalamide B **1.5** we examined the route to determine how successful we had been in reaching our objectives set in Chapter 2. We thought the early part of the synthesis up to the dihydropyranone **2.2** needed no alteration; the chemistry was efficient, suitable for large scale, avoided the use of column chromatography and the dihydropyranone **2.2** showed promise as a versatile intermediate. The next section of the synthesis to the diol **2.1** was also efficient and suitable for moderate scale work, however the C-15 side chain functionality was introduced by this point. The synthesis would have been more versatile if the C-15 side chain functionality had been introduced later on, ideally after the left and right fragments had been coupled together. The last section of the right fragment synthesis of 18-*O*-methyl mycalamide B was similar to that which had already been described in the literature. We believed there were three areas of the right fragment (**1.57**) synthesis that need further attention; 1) the construction of the 2,4,7-trioxabicyclo[4.4.0]decane ring from diol **2.1** was a long sequence, requiring a 3 step protection-deprotection strategy to select a primary alcohol over a secondary alcohol for

further elaboration; 2) the use of $HCl_{(g)}$ in conjunction with paraformaldehyde to form the 1,3-dioxane ring **5.22a,b** were very harsh conditions limiting other possible versatile functionalities in the C-15 side chain and 3) the creation of oxalamide **1.57** *via* azide **5.24** gave only a 1:2 mixture of diastereoisomers in favour of the undesired oxalamide **1.71** in 57% yield. The lack of diastereocontrol and low yield in the last two steps of the right fragment synthesis caused the loss of 81% of material, which was clearly unacceptable and should be improved.

After the above evaluation of the 18-*O*-methyl mycalamide B synthesis we decided to design a new synthesis to tackle the problems outlined above. We chose theopederin D (**1.1d**) as our target because it had never been synthesised before and the lactone functionality in the C-15 side chain would dominate our approach forcing us to develop a more versatile C-15 side chain. The route is described in chapter 6 of this thesis.

Chapter 6

Synthesis of Theopederin D

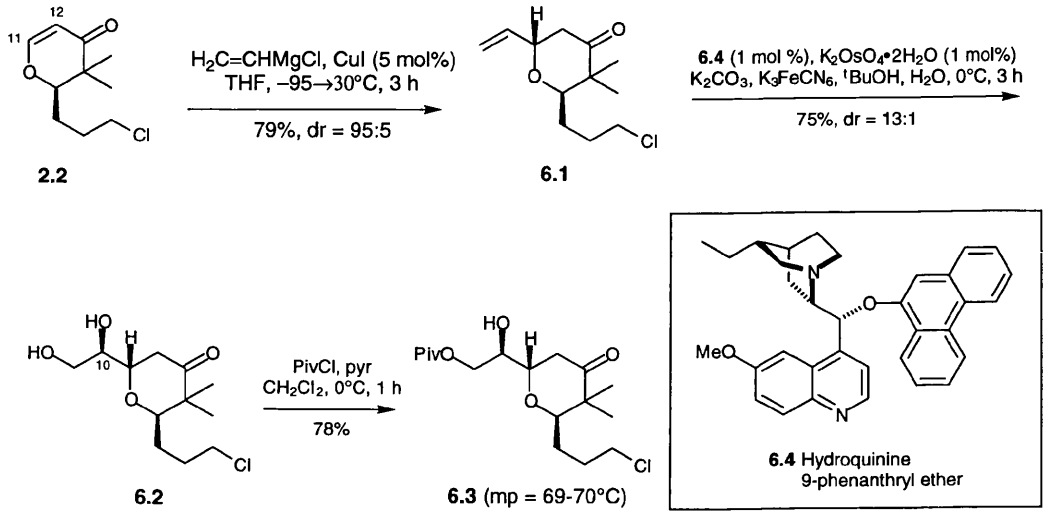


Our experiences from the 18-*O*-methyl mycalamide (**1.5**) synthesis (chapter 5) caused us to develop a new approach to theopederin D (**1.1d**) in order to meet all our objectives set in Chapter 2. We also concluded that the synthesis of the early intermediate **2.2** met all of our objectives and therefore was a logical point to begin. In the light of the success of Hoffmann[20] and Roush[25] in introducing the C-10 aminal centre stereoselectively *via* a Curtius rearrangement, we decided to direct our second generation route towards an intermediate suitable for a Curtius rearrangement. In order to give the versatility required to enable us to synthesise any of the theopederins A-E **1.1a-e**[1], onnamide A **1.2**[4], and mycalamide A **1.3**[2] we incorporated a terminal olefin in the C-15 side chain which would serve as a "synthetic handle" for further elaboration. Our new approach is based on four key steps: 1) diastereoselective 1,4-conjugate addition of vinyl Grignard to dihydropyranone **2.2**; 2) reaction of a methoxymethyl ether with a silyloxirane induced by phosphorous pentoxide; 3) Curtius rearrangement and trapping of the isocyanate intermediate with trimethylsilylethanol; 4) addition of a three carbon fragment to an aldehyde.

6.1 Introduction of the Stereogenic Centres at C-10 and C-11

We chose to introduce a two carbon fragment at C-11 *via* a copper(I)-catalysed 1,4-addition of vinylmagnesium chloride to dihydropyranone **2.2**, which proceeded with good 1,3-asymmetric control to give olefin **6.1** in 79% yield (scheme 6.1). A 15:1 mixture of diastereoisomers at C-11 was determined by ^{1}H NMR spectroscopic analysis by integration of the two doublet of doublet signals derived from C12-H_2 [^{1}H NMR, (360 MHz, $CDCl_3$): δ = 2.85 and 2.81 (minor) and 2.55 and 2.67 (major) ppm]. A rationale for the good diastereocontrol of the 1,4-addition is the same as that given in chapter 5 for a similar transformation (scheme 5.1) and a stereochemical assignment of (11*S*) was made, also based

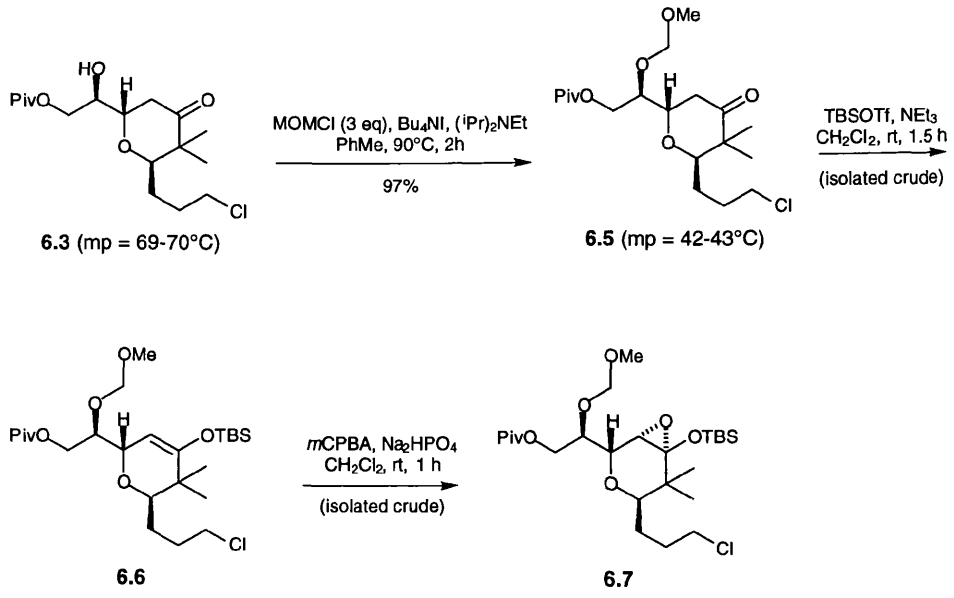
on a 1,4-addition to dihydropyranone **2.2** shown in scheme 5.1. Asymmetric dihydroxylation was used to convert olefin **6.1** to diol **6.2** in 75% yield employing hydroquinine 9-phenanthryl ether **6.4** as the chiral ligand.[100] A 13:1 mixture of diastereoisomers at C-10 was obtained as determined by ^{1}H NMR spectroscopic analysis by integration of signals derived from C14-Me [^{1}H NMR (360 MHz, $CDCl_3$): δ = 1.28 ppm (minor) and 1.26 ppm (major)]. The primary alcohol of the diol **6.2** was selectively protected as its pivalate ester **6.3** which was highly crystalline allowing removal of all minor diastereomeric impurities by a single recrystallisation.



Scheme 6.1

6.2 Construction of the Cis-2,4,7-trioxabicyclo[4.4.0]decane Ring

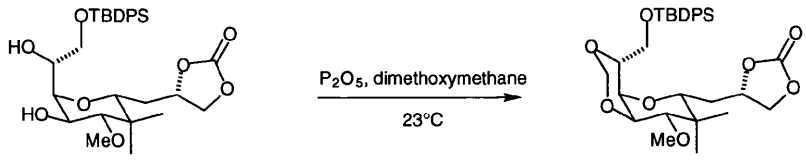
Conversion of **6.3** to epoxide **6.7** is outlined in scheme 6.2.



Scheme 6.2

The methoxymethyl ether (**6.5**) required for 1,3-dioxane formation was obtained as a white crystalline solid from the alcohol **6.3** in 97% yield (scheme 6.2). A standard transformation converted the ketone **6.5** to the enol silane **6.6** which was subjected to epoxidation conditions. Dimethyl dioxirane generated *in situ*[58,59] under phase transfer conditions[60] (as used during our synthesis of 18-*O*-methyl mycalamide, chapter 5, scheme 5.2) gave oxirane **6.7** as a 3:1 mixture of diastereoisomers as determined by ^{1}H NMR spectroscopic analysis. However, *m*CPBA epoxidation conditions returned the same oxirane **6.7** as a single diastereoisomer. A rationale for the excellent stereoselectivity achieved by the epoxidation of enol silane **6.6** is the same as that given for the epoxidation of enol silane **1.65** in Chapter 5 (scheme 5.3 and 5.4). Assignment of the oxirane (**6.7**) stereochemistry was made after the next step (*vide infra*).

During a synthesis of the trioxadecalin nucleus of mycalamide A Roush[44] reported the generation of the methylene acetal in **6.9** by adding phosphorous pentoxide (P_2O_5) to a solution of diol **6.8** in dimethoxymethane[101] as shown in scheme 6.3.



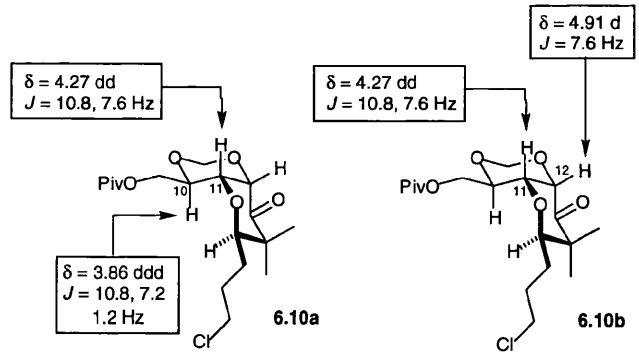
6.8 **6.9**

Scheme 6.3

Adopting similar conditions (scheme 6.4), we were pleased to find that the addition of oxirane **6.7** to a large excess of dimethoxymethane and P_2O_5 at 0°C caused ring closure to form the 2,4,7-trioxabicyclo[4.4.0]decane ring system in 77% yield after 3 steps and ^1H NMR spectroscopic analysis showed a favourable diastereomeric ratio of 15:1 at C-12 by integration of signals derived from C14-Me singlets [^1H NMR (360 MHz, $CDCl_3$): δ = 1.32 ppm (minor) and 1.06 ppm (major)]. A notable observation is that if the phosphorous pentoxide is added to a stirred solution of oxirane **6.7** and dimethoxymethane at 0°C, the desired 2,4,7-trioxabicyclo[4.4.0]decane ring system is formed with a lower diastereomeric ratio of 8:1 at C-12 in 70% yield.

6.7 **6.10** (mp = 88-89°C)

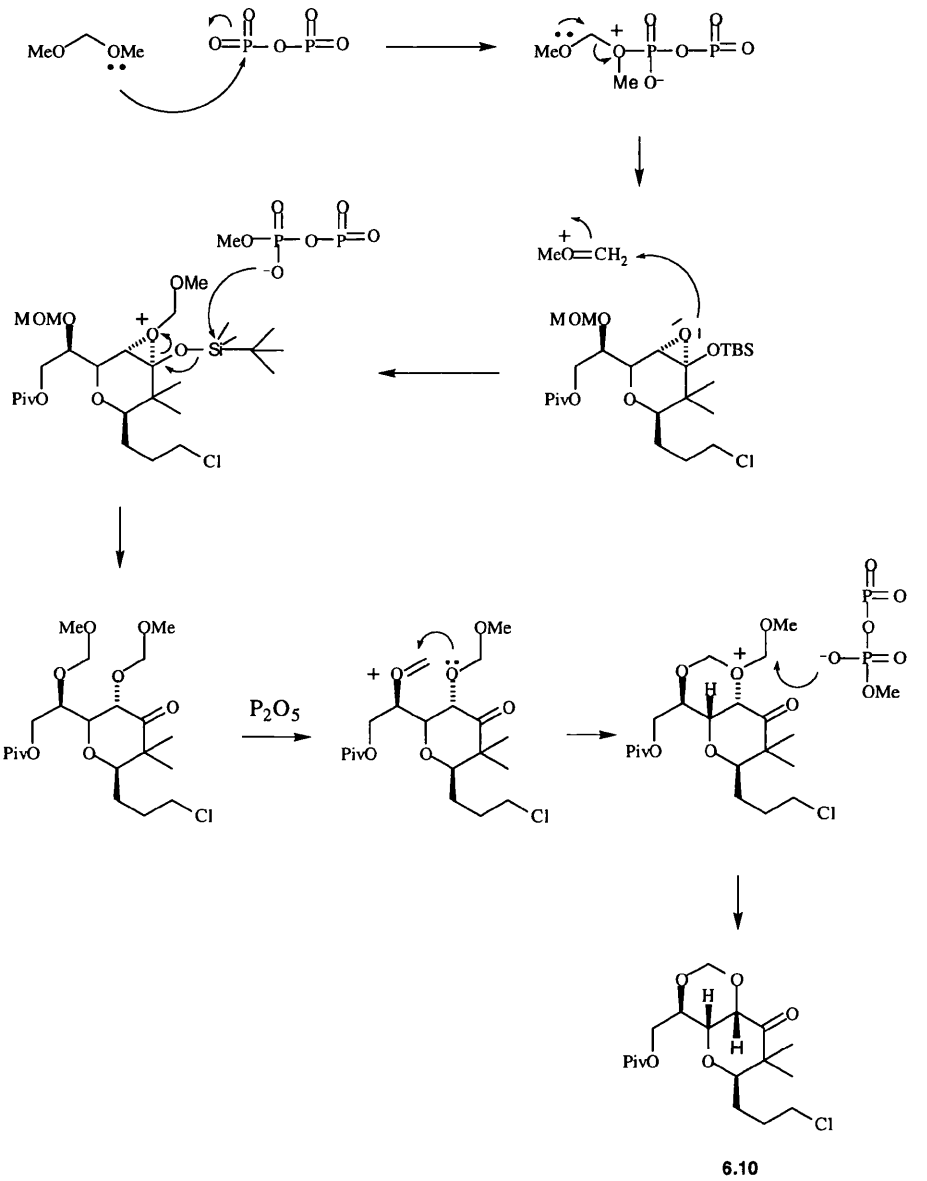
Assignment of relative stereochemistry by ^1H NMR spectroscopic analysis



6.10a **6.10b**

Scheme 6.4

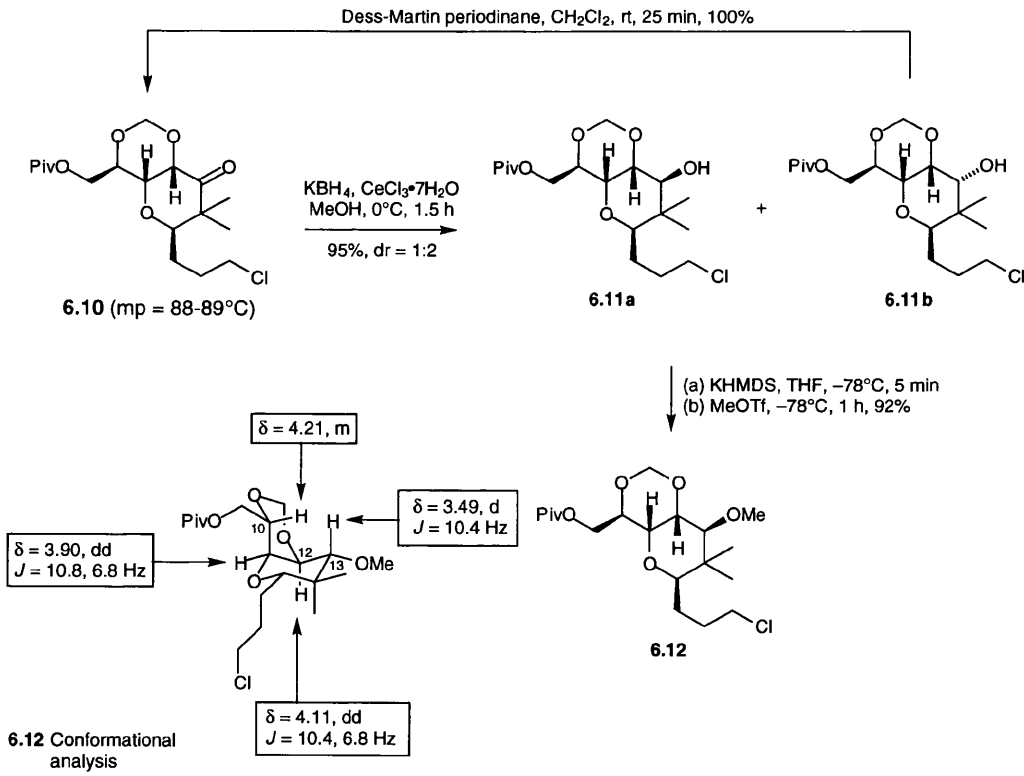
A *trans*-diaxial relationship between the protons of C-10 and C-11 was determined by examination of the C10-H and C11-H vicinal coupling constants (10.8 Hz) in the ^{1}H NMR spectra of **6.10** thus proving the relative stereochemistry at C-10 (see **6.10a** scheme 6.4). Examination of the vicinal coupling constants between C11-H and C12-H (7.6 Hz) showed the formation of a *cis*-declin ring as opposed to a *trans*-declin ring thus proving the relative stereochemistry at C-12 (see **6.10a** in scheme 6.4). A tentative assignment of (12*S*) absolute stereochemistry was made which was confirmed later on during our synthesis (*vide infra*). A mechanism for the P_2O_5 reaction is proposed in scheme 6.5



Scheme 6.5

6.3 Formation of the C-13 Stereogenic Centre

Stereoselective reduction of ketone **6.10** proved problematic. The best diastereoselectivity obtained was 1:2 in favour of the undesired diastereoisomer **6.11b** using an excess of KBH_4 and $CeCl_3 \cdot 7H_2O$ in methanol at 0°C (scheme 6.6). ^1H NMR analysis of crude product showed the 1:2 ratio of diastereoisomers at C-13 by integration of signals derived from C14-Me [^1H NMR (360 MHz, $CDCl_3$): δ = 1.14 ppm (major) and 1.05 ppm (minor)]. A wide range of hydride reducing agents were investigated ($NaBH_4$, $NaH(OAc)_3$, $Na(CN)BH_3$, $BH_3 \cdot THF$, L-selectride, $LiAlH_4$, and KBH_4) but they gave poor selectivity as did other methods involving single electron transfer. Na-EtOH and SmI_2-^{i}PrOH caused destruction of the ketone **6.10** and Mg-MeOH gave a 1:1 mixture of alcohols with concomitant reduction of chloride at C-18. To overcome the problem of poor selectivity and make desired material we separated the diols **6.11a** and **6.11b** by column chromatography (easily separable) and oxidised the undesired diol **6.11b** using Dess-Martin periodinane reagent[98] back to ketone **6.10**. The ketone **6.10** was then reduced again as described and the whole cycle repeated. *O*-Methylation of **6.11a** returned **6.12** in 92% yield.



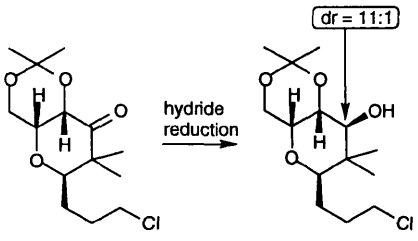
Scheme 6.6

Examination of the ^1H NMR spectroscopic vicinal coupling constants between C10-H and C11-H (10.8 Hz); C11-H and C12-H (6.8 Hz); C12-H and C13-H (10.4 Hz) define the conformation of **6.12** (scheme 6.6). The C-12 and C-13 protons adopt a *trans*-diaxial

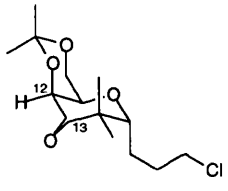
conformation as do the C10 and C11 protons and the C11 and C12 protons adopt an equatorial-axial relationship relative to one another. The absolute stereochemistry at C-10, C-11 and C-12 was tentatively assigned (10*R*,11*R*,12*S*) from previous conformational analysis of **6.10** thus the absolute stereochemistry of **6.12** at C-13 was tentatively assigned as (13*S*).

It was striking that the diastereoselectivity observed in the reduction of ketone **6.10** using hydride reducing agents was so poor when compared to that of a similar ketone **5.8** using $NaBH(OAc)_3$ and $CeCl_3 \cdot 7H_2O$ during our synthesis of 18-*O*-methyl mycalamide B (dr = 11:1, chapter 5, scheme 5.6). Comparison of the conformers of the two ketones **6.10** and **5.8** in scheme 6.7 offers an explanation. Ketone **5.8** adopted a conformation with the C-15 side chain in an axial position which allowed intramolecular equatorial delivery of the hydride *via* a chelation between the boron and the axial α-alkoxy of the isopropylidene **5.9c**. However, we have shown (scheme 6.4, **6.10a** and **6.10b**) that ketone **6.10** adopted a conformation with the C-15 side chain in an equatorial position and it was apparent that there were no proximate oxygens in the dioxane ring thereby preventing intramolecular delivery of hydride. Therefore, the hydride attacked ketone **6.10** from the equatorial direction in the conformer shown in scheme 6.7, being the least hindered direction of attack, resulting in the formation of the unnatural stereochemistry at C-13.

18-*O*-Methyl mycalamide series

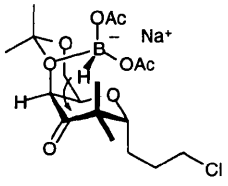


5.8 **5.9a,b**



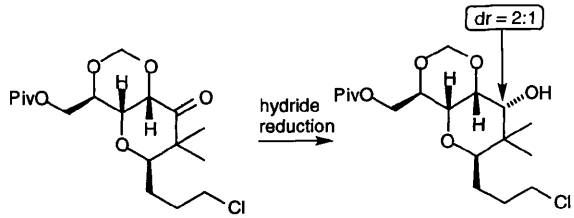
5.8

C-15 side chain in
an axial postion

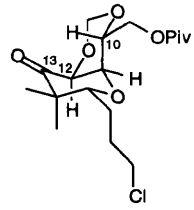


5.9c Intramolecular delivery
of hydride

Theopederin D series

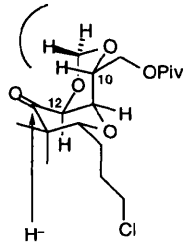


6.10 (mp = 88-89°C) **6.11a,b**



6.10

C-15 side chain in
an equatorial postion

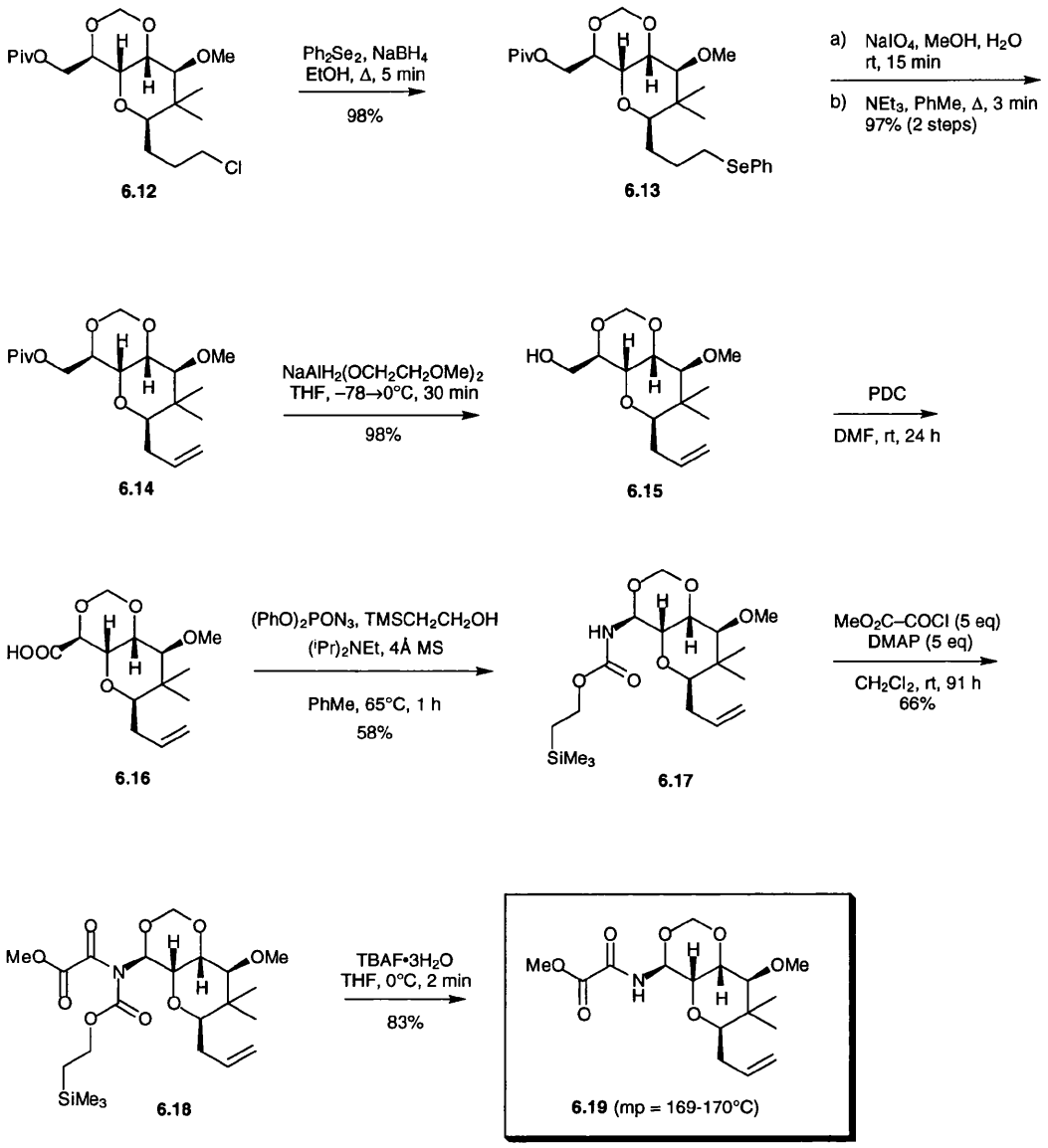


Equatorial attack of hydride

Scheme 6.7

6.4 Completion of the Right Fragment Synthesis

Conversion of **6.12** to **6.19** is presented in scheme 6.8.



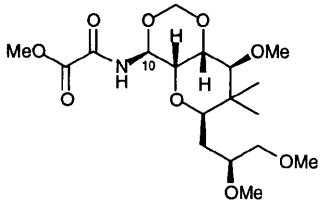
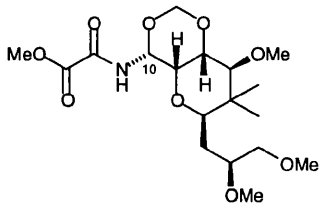
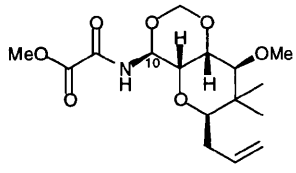
Scheme 6.8

Introduction of the C-10 stereogenic centre was preceded by installation of a terminal olefin in the C-15 side chain as a versatile synthetic handle. Chloride **6.12** was converted to olefin **6.14** *via* selenide **6.13** using conditions previously described (chapter 5, scheme 5.9) in 95% yield over 3 steps. Reductive cleavage of pivalate **6.14** using Red-Al occurred in excellent yield (98%) to give the alcohol **6.15**. Reductive cleavage of pivalate **6.14** using DIBAL suffered from poor yields probably due to the strong chelation of the aluminium to the 5 oxygen atoms in **6.15**. Oxidation of alcohol **6.15** to the carboxylic acid **6.16** required stirring with pyridium dichromate in DMF at room temperature for 24 hours. The carboxylic acid

6.16 was used to create the C-10 aminal *via* a Curtius rearrangement using the conditions of Shioiri.[53] Preparation of the acyl azide by reaction of carboxylic acid **6.16** with diphenylphosphoryl azide followed by thermolysis in the presence of 2-(trimethylsilyl)ethanol to trap the intermediate isocyanate furnished the 2-(trimethylsilyl)ethyl carbamate **6.17**.[44] One diastereoisomer was observed by ^{1}H NMR spectroscopy whose stereochemistry was assigned after a further two steps. Acylation of carbamate **6.17** occurred cleanly albeit slowly using methyl oxalyl chloride and DMAP to give the *N*-acyl oxalamide **6.18** in 66% yield. Fluoride-induced cleavage of the 2-(trimethylsilyl) carbamate **6.18** released oxalamide ester **6.19**, the right fragment, as a white solid[27].

The stereochemistry at C-10 was assigned as (10*S*) by comparison of the characteristic C10-H signals in the ^{1}H NMR spectra of **6.17** with the C10-H signals of the reported oxalamides **1.57** and **1.71**.[17] The natural (10*S*) configuration has a characteristic C-10 triplet at δ = 5.78 (1H, t, J = 9.7 Hz), see scheme 6.9.

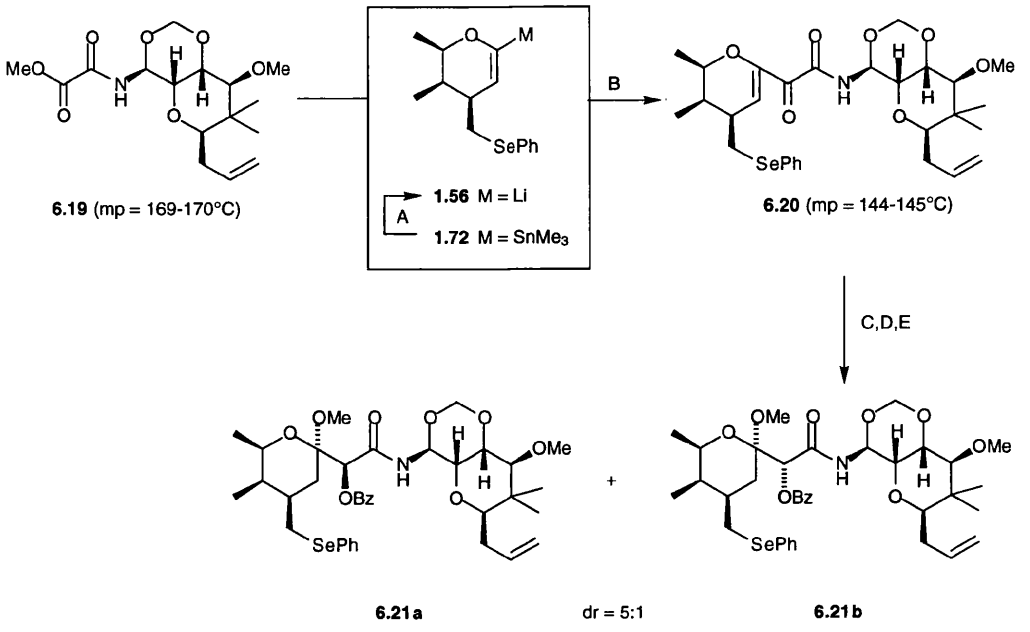
Comparison of published ^{1}H NMR data (270 MHz, $CDCl_3$, ref 7.27 ppm) for **1.57** and **1.71** with ^{1}H NMR data (360 MHz, $CDCl_3$, ref 7.27 ppm) for theopederin D intermediate **6.19**

Natural configuration at C-10	Unnatural configuration at C-10	Comparison to theopederin D intermediate
		
1.57	**1.71**	**6.19**
δ = 7.58 (1H, br d, J = 9.1 Hz, **NH**)	δ = 8.19 (1H, br d, J = 9.5 Hz, **NH**)	δ = 7.53 (1H, br d, J = 9.2 Hz, **NH**)
δ = 5.71 (1H, t, J = 9.8 Hz, **C10-H**)	δ = 5.44 (1H, dd, J = 1.7, 9.8 Hz, **C10-H**)	δ = 5.73 (1H, t, J = 9.7 Hz, **C10-H**)

Scheme 6.9

6.5 Construction of the *N*-(1-alkoxy-1-alkyl)amide Bridge and Creation of C-7 Stereogenic Centre

Prior to our synthesis of theopederin D the coupling of the left and right fragments of the mycalamides had proved capricious. However, a yield of >70% was obtained three times in succession demonstrating the coupling reaction to be reproducible (scheme 6.10). We believe the drying of both **1.56** and **6.19** by azeotropic distillation from toluene and the rigorous drying of all glassware and needles is the key to performing the coupling reaction in >70% yield.



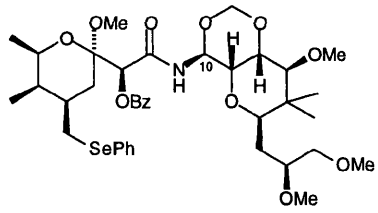
Scheme 6.10 *Reagents and conditions:*

A	↓	stannane **1.72** (3 eq), ^{n}BuLi, THF-hexanes, –78°C, 15 min
B	78%	TMEDA, ester **6.19**, THF, –78°C, 2 h
C	↓	*s*-Bu_3BHLi, THF, –95°C, 15 min
D	↓	CSA, MeOH–CH_2Cl_2, rt, 40 min
E	91%	BzCl, DMAP, $(^{i}Pr)_2NEt$, CH_2Cl_2, rt

71.0 % overall yield (5 steps)

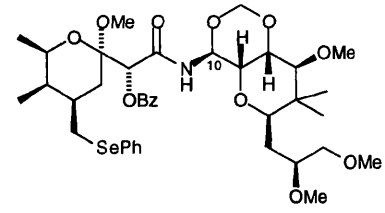
Three equivalents of vinyl stannane **1.72** were transmetallated to the lithium derivative **1.56** with ^{n}BuLi at –78°C in THF (scheme 6.10). To the mixture was added *N,N,N',N'*-tetramethylethylenediamine (TMEDA) followed by a THF solution of oxalamide **6.19** at –78°C. The acylated dihydro-2*H*-pyran derivative **6.20** was formed in 78% yield as a colourless crystalline solid. Reduction of the ketone **6.20** with LiBH(*s*-Bu)$_3$ at –95°C followed by acid-catalysed diastereoselective addition of MeOH to the dihydropyran and benzoylation gave benzoates **6.21a** and **6.21b**. A 5:1 ratio of diastereoisomers at C-7 was obtained as determined by ^{1}H NMR spectroscopic analysis by integration of doublets derived from the OCH_AH$_B$O signal [^{1}H NMR (360 MHz,C_6D_6, referenced to 7.16 ppm): δ = 4.53 (major) and 4.71 (minor)]. The two diastereoisomers were assigned (6*R*,7*S*) for **6.21a** and (6*R*,7*R*) **6.21b** (scheme 6.11) based on a comparison of the ^{1}H NMR spectroscopic C10-H chemical shifts of **6.21a** and **6.21b** with the ^{1}H NMR spectroscopic C10-H chemical shifts for benzoates **1.74a** and **1.74b**, which were previously observed during our synthesis of 18-*O*-methyl mycalamide B **1.5**.

Comparison of published ^{1}H NMR data (360 MHz, C_6D_6, ref 7.16 ppm) for benzoates **1.74a** and **1.74b** with ^{1}H NMR data (360 MHz, C_6D_6, ref 7.16 ppm) for benzoates **6.21a** and **6.21b**



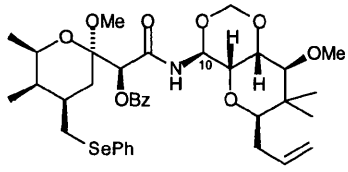
1.74a

δ = 5.93 (1H, t, *J* = 9.7 Hz, C10-H)



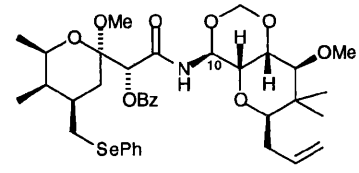
1.74b

δ = 5.97 (1H, t, *J* = 9.7 Hz, C10-H)



6.21a

δ = 5.94 (1H, t, *J* = 9.7 Hz, C10-H)



6.21b

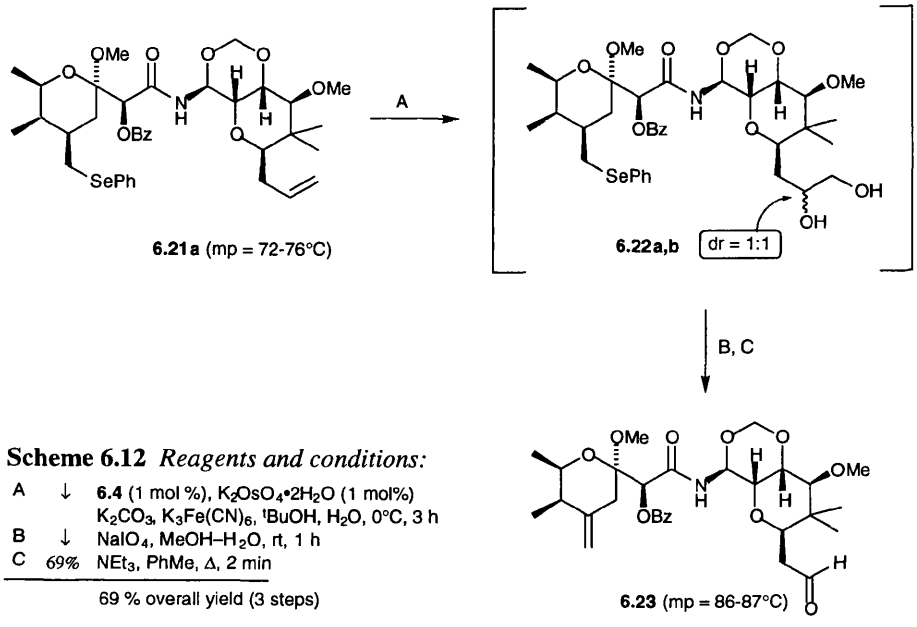
δ = 6.02 (1H, t, *J* = 9.7 Hz, C10-H

Scheme 6.11

The acylated dihydro-2*H*-pyran derivative **6.20** was crystallised and its X-ray crystal structure determined. The presence of the selenium atom allowed the absolute stereochemistry of **6.20** to be defined and we were pleased to confirm that all our tentative stereochemical assignments were correct; (2*R*,3*R*,4*S*,10*S*,11*S*,12*R*,13*S*,15*R*) **Figure 1**. Bond lengths and bond angles are given in appendix A of this thesis.

6.6 Synthesis of Theopederin D (1.1d) and 17-epi-Theopederin D (6.27)

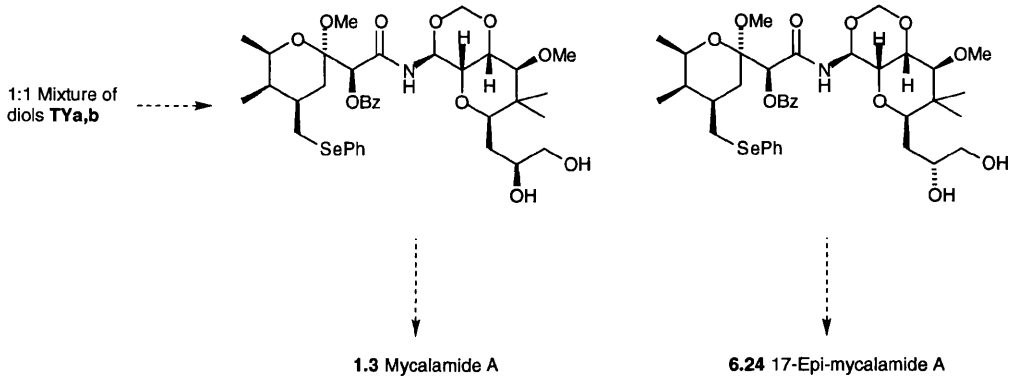
Asymmetric dihydroxylation converted olefin **6.21a** (scheme 6.12) to an approximate 1:1 mixture of diastereomeric diols **6.22a,b**, as determined by TLC, using hydroquinine 9-phenanthryl ether **6.4** as ligand[100] and we were pleased to observe no complications from the selenium atom. The diols **6.22a,b** were separable by TLC (hexanes:EtOAc 3:7) but for our purposes separation of diastereoisomers was of no consequence as the diols **6.22a,b** were cleaved to an aldehyde function using sodium metaperiodate. During diol cleavage the selenide function was oxidised to its corresponding selenoxide, which on refluxing in a mixture of toluene and triethylamine returned the exocyclic methylene to give aldehyde **6.23** in 69% yield.



Scheme 6.12 *Reagents and conditions:*

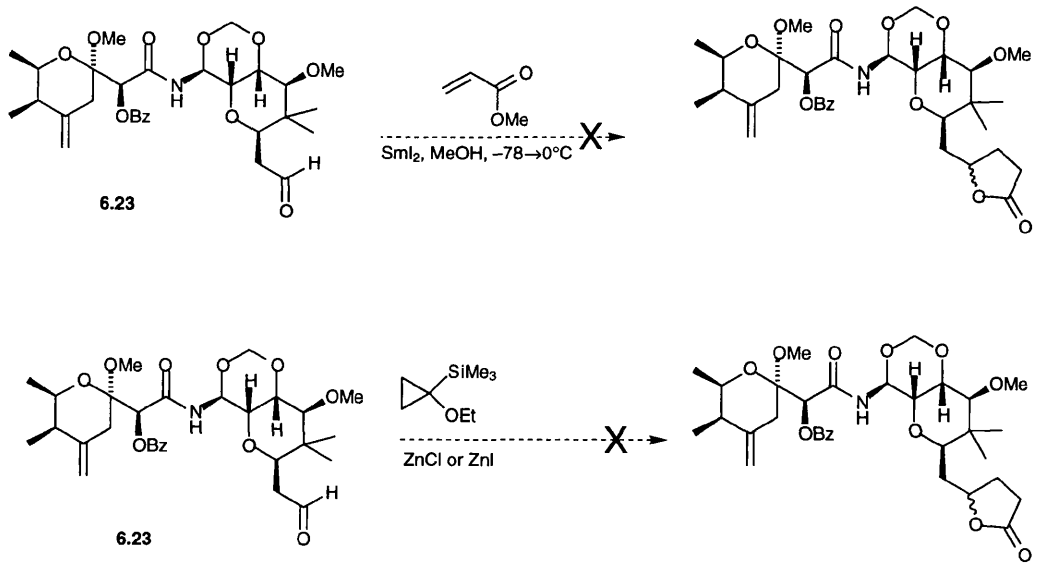
A	↓	**6.4** (1 mol %), $K_2OsO_4 \cdot 2H_2O$ (1 mol%) K_2CO_3, $K_3Fe(CN)_6$, ^tBuOH, H_2O, 0°C, 3 h
B	↓	$NaIO_4$, MeOH–H_2O, rt, 1 h
C	69%	NEt_3, PhMe, Δ, 2 min
		69 % overall yield (3 steps)

At this stage it is worth noting that the 1:1 diastereomeric mixture of diols **6.22a,b** could have been separated by column chromatography and converted to mycalamide A **1.3** and 17-epi-mycalamide A **6.24** (scheme 6.13). However, owing to the lack of time and material, these transformations were not performed.



Scheme 6.13

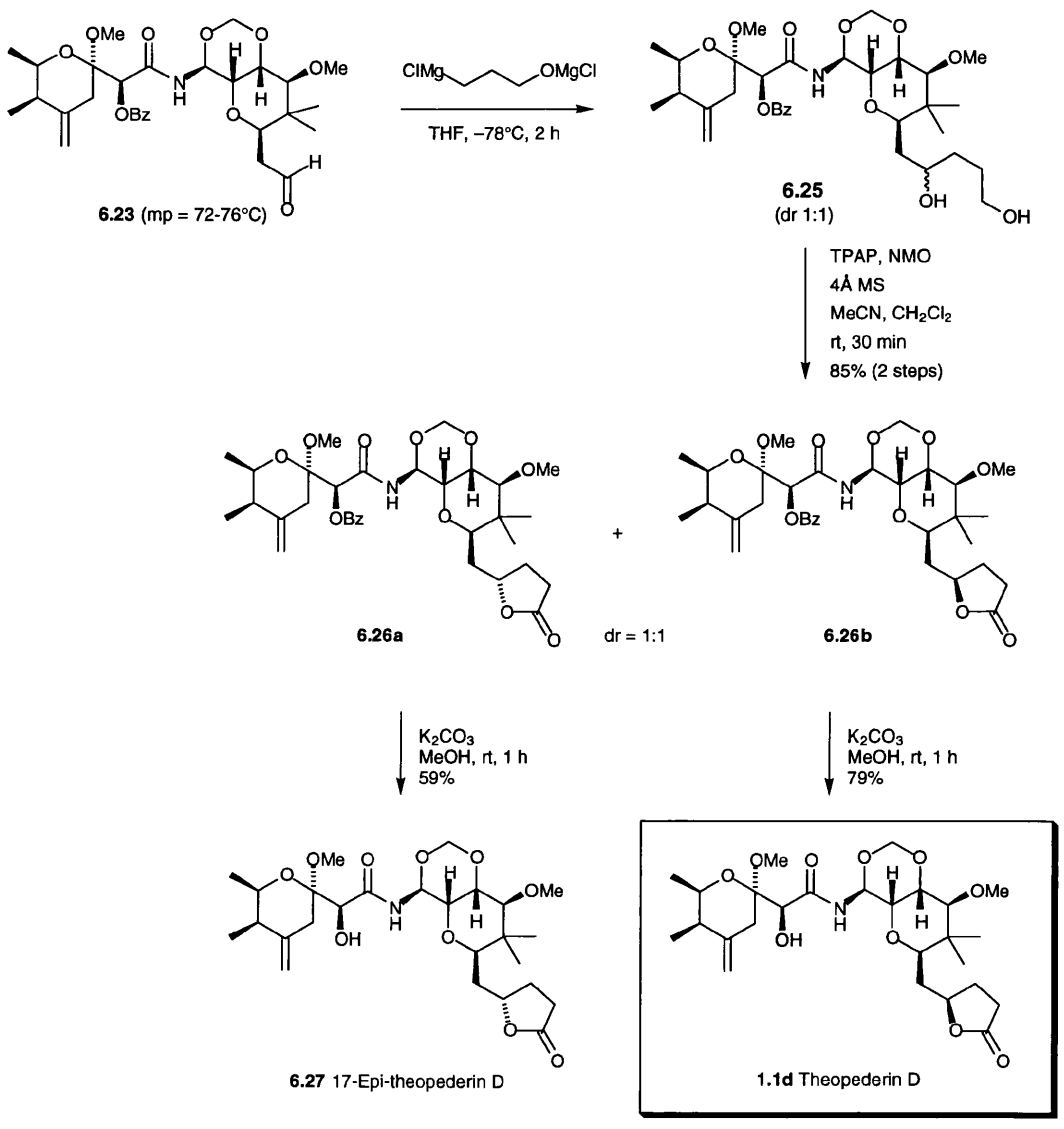
The choice of methods for introducing a suitable 3 carbon fragment to form the butyrolactone were severely restricted due to the acid sensitivity of the homoallylic acetal. Attempts to introduce a propionate component directly by addition of 2-carboethoxyethylzinc[102] or samarium reagents[103] gave complex mixtures and are summarised in scheme 6.14.



Scheme 6.14

However, a Grignard reagent derived from unprotected 3-chloropropan-1-ol[104] added to aldehyde **6.23** cleanly at –78°C to furnish the 1,4-diols **6.25** (scheme 6.15). Oxidation of a crude mixture of diols **6.25** with TPAP[105,106] gave butyrolactones **6.26a,b** in 85% yield and ^{1}H NMR spectroscopic analysis showed a 1:1 mixture of diastereoisomers at C-17 by integration of C7-H singlets [^{1}H NMR (360 MHz, C_6D_6, referenced to 7.16 ppm): δ = 5.94 and 5.84 ppm]. The diastereoisomers were separated by preparative TLC. Finally, methanolysis of the benzoate ester **6.26a** using potassium carbonate in methanol gave theopederin D as determined by comparison of the ^{1}H and ^{13}C NMR spectra (400 MHz and 100 MHz respectively) with published data for the natural product (**Table 1** and **2**)[1]. 17-Epi-

theopederin D **6.27** was prepared using the same conditions as described above (scheme 6.15) and was clearly distinguishable by ^{1}H and ^{13}C NMR spectroscopy.



Scheme 6.15

Table 1. ^{1}H NMR Data for Synthetic and Natural Theopederin D

	Synthetic		Natural	
Position	δ_H	J (Hz)	δ_H	J (Hz)
2	4.03 (dq)	6.5, 2.7	4.01 (dq)	6.6, 2.8
2-Me	1.20 (d)	6.5	1.18 (d)	6.6
3	2.26 (dq)	7.1, 2.7	2.24 (dq)	7.1, 2.6
3-Me	1.01 (d)	7.1	0.98 (d)	7.1
4	—	—	—	—
4=CH_2	4.86 (br s)	—	4.84 (t)	1.7
	4.74 (br s)	—	4.73 (t)	1.7
5	2.35 (d)	14.0	2.33 (d)	13.9
	2.21 (bd)	14.0	2.18 (d)	14.1
6	—	—	—	—
6-OMe	3.28 (s)	—	3.28 (s)	—
7	4.27 (d)	3.1	4.25 (d)	3.2
7-OH	4.08 (d)	3.1	4.11 (d)	3.2
8	—	—	—	—
9-NH	7.52 (d)	9.4	7.51 (d)	10.3
10	5.81 (dd)	9.4, 9.4	5.80 (dd)	9.5, 9.5
10-OCH_2O	5.13 (app d)	7.0	5.11 (app d)	7.0
	4.87 (app d)	7.0	4.86 (app d)	7.0
11	3.82 (dd)	9.4, 6.4	3.80 (dd)	9.2, 6.4
12	4.21 (dd)	10.2, 6.4	4.19 (dd)	9.7, 6.4
13	3.44 (d)	10.2	3.42 (d)	9.5
13-OMe	3.56 (s)	—	3.54 (s)	—
14	—	—	—	—
14-Me (ax)	1.02 (s)	—	1.00 (s)	—
14-Me (eq)	0.88 (s)	—	0.86 (s)	—
15	3.42 (d)	10.2	3.40 (d)	9.0
16	1.59 (dd)	14,2, 8.3	1.58 (ddd)	14.3, 8.3, 1.3
	1.94 (m)	—	1.92 (m)	—
17	4.45 (ddd)	14.2, 8.4, 6.0	4.42 (ddd)	14.1, 8.2, 5.9
18	1.75 (2H, m)	—	1.76 (2H, m)	—
19	2.51 (ddd)	17.6, 10.0, 3.8	2.50 (m)	—
	2.45 (dd)	17.6, 11.1	2.45 (m)	—
20	—	—	—	—

Table 2. ^{13}C NMR Data for Synthetic and Natural Theopederin D

	Synthetic	Natural
Position	δ_C	δ_C
2	69.4	69.6
2-Me	17.4	18.0
3	41.1	41.3
3-Me	11.5	12.0
4	144.6	145.0
4=CH_2	111.0	111.0
5	32.9	33.3
6	99.7	99.8
6-OMe	48.2	48.5
7	71.5	71.6
8	171.7	172.3
10	73.4	73.6
10-OCH_2O	86.4	86.5
11	70.0	69.5
12	73.9	74.0
13	79.2	79.5
13-OMe	61.4	61.7
14	41.1	41.1
14-Me (ax)	13.5	14.1
14-Me (eq)	23.0	23.6
15	75.8	76.0
16	34.6	35.0
17	79.1	79.2
18	27.6	28.0
19	28.1	28.7
20	176.7	177.5

A copy of the ^1H and ^{13}C NMR spectra of synthetic theopederin D is shown in appendix C. A comparison of the ^1H NMR spectra of synthetic theopederin D with a ^1H NMR spectra of natural theopederin D is also shown in appendix C.

6.7 Conclusion

Advanced intermediates **1.72** and **6.19** were synthesised from cheap readily available starting materials in 14 steps (12.7% yield) and 20 steps (4.5% yield) respectively. **1.72** and **6.19** were coupled together and converted to theopederin D in 10 steps (37.8% yield) installing the butyrolactone at the last stage of the synthesis.

Chapter 7

Closing Remarks

The aim of the study was to synthesise theopederin D **1.1d** as efficiently as possible starting from readily available starting materials. From the outset we planned; 1) to include a metallated dihydropyran approach to couple the left and right fragments together; 2) to develop an efficient, highly enantioselective, large scale route to early intermediates of the right fragment **6.19** and 3) to develop a new and more efficient route towards the left fragment **1.72**.

In order to conduct the study we chose 18-*O*-methyl mycalamide B **1.5** as our initial target, for **1.5** had already been synthesised within the Kocienski group and would help expedite our study towards theopederin D. A synthesis of 18-*O*-methyl mycalamide B was completed (see chapter 5) encompassing all we had planned from the outset. However, after evaluating the new route to 18-*O*-methyl mycalamide B we concluded the route towards the right fragment was too long, the diastereocontrol at the C-10 stereogenic centre was poor and the conditions employed to construct the *cis*-2,4,7-trioxabicyclo[4.4.0]decalin ring were very harsh (HCl gas). Thus a new route to the right fragment of theopederin D was developed using dimethoxymethane/P_2O_5 in conjunction with the epoxide **6.7** to construct the *cis*-2,4,7-trioxabicyclo[4.4.0]decalin ring and a Curtius rearrangement to install the stereogenic centre at C-10. After coupling the left and right fragments **1.72** and **6.19** using a metallated dihydropyran approach, the butyrolactone functionality was installed by addition of a Grignard reagent, derived from unprotected 3-chloropropan-1-ol, to aldehyde **6.23** followed by TPAP oxidation. A schematic summary of the synthetic route to theopederin D is given in last page of this thesis.

Chapter 8

Experimental

7.1 General Experimental Details

Reactions requiring anhydrous conditions were conducted in flame-dried apparatus under a static atmosphere of dry argon or nitrogen. Organic extracts were evaporated at electric pump (5-10 mm Hg) or water pump (20 mm Hg) using a Buchi rotary evaporator.

Where appropriate, solvents and reagents were dried by standard methods,[107] *i.e.* by distillation from the usual drying agent prior to use: diethyl ether and tetrahydrofuran were distilled from Na/benzophenone and used fresh. Acetonitrile, pentane, pyridine, dichloromethane, *N*,*N*-dimethylformamide, toluene and triethylamine were distilled from CaH_2 and stored over 4 Å molecular sieves under nitrogen. Methanol was distilled from the corresponding magnesium alkoxide. Hexanes (bp 40-60°C) for chromatography was distilled before use. Trimethylsilyl chloride was distilled freshly before use. Iodine was sublimed at 0.5 mg Hg and stored under nitrogen. For best results, copper (I) iodide was extracted with THF in a soxhlet apparatus and stored in the dark. The Dess-Martin periodinane reagent[98,108] was prepared according to the literature and stored at –20°C under nitrogen. Commercial organometallics were used as supplied and alkyllithium reagents were titrated against 1,3-diphenylacetone *p*-tosylhydrazone.[109]

All reactions were magnetically stirred and were monitored by Thin Layer Chromatography (TLC) using Macherey-Nagel Düren Alugram Sil G/UV_{254} pre-coated aluminium foil sheets, layer thickness 0.25 mm. Compounds were visualised by UV (254 nm), 20 wt% phosphomolybdic acid (PMA) in ethanol with heating, anisaldehyde with heating, vanallin followed by H_2SO_4 with heating, potassium permanganate with heating or Ceric sulphate with heating. Flash chromatography was performed on Merck silica gel 60 (0.04-0.063 mm, 230-400 mesh) and run under low pressure.[110]

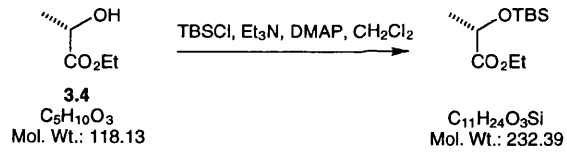
Optical rotations were recorded on an Optical Activity AA-100 polarimeter. Melting points were measured on a Griffin electrothermal apparatus and are uncorrected. IR spectra were recorded on a Perkin Elmer 1600 series FTIR spectrometer as thin films supported on sodium chloride plates. Absorptions are reported as values in cm^{-1} and defined as either strong (s), medium (m). Broad absorptions are designated (br). Weak absorptions are not reported.

Proton NMR spectra were recorded in Fourier Transform mode on a Jeol JNX-GX 270 (270 MHz), Bruker AM 300 (300 MHz), Bruker AM 360 (360 MHz) or Bruker DPX 400 (400 MHz) spectrometer in either chloroform-*d* or benzene-d_6. Chemical shifts are reported in ppm relative to residual $CHCl_3$ (δ = 7.27) or benzene (δ =

7.16). Multiplicities are described using the following abbreviations: (s) singlet, (d) doublet, (t) triplet, (q) quartet, (m) multiplet, (br) broad. The nomenclature used for the assignment of individual protons within a given spectra was based on the theopederin D numbering shown in scheme 1.1 of this thesis. Carbon-13 NMR spectra were recorded on a Jeol JNX-GX-270 (68 MHz), Bruker AM 300 (75 MHz), Bruker AM 360 (90 MHz) or Bruker DPX 400 (100 Hz) spectrometer in either chloroform-*d* (δ = 77.2) or benzene-d_6 (δ = 128.7). Chemical shifts are reported in ppm relative to the solvent. Multiplicities were determined using the Distortionless Enhancement by Phase Transfer (DEPT) spectral editing technique, with secondary pulses at 90° and 135°. C-H coupling is indicated by an integer 0-3 in parenthesis following the ^{13}C chemical shift value denoting the number of coupled protons. Mass spectra were run on a VG 70-250-SE or JEOL MStation JMS-700 spectrometer. Ion mass/charge (*m/z*) ratios are reported as values in atomic mass units followed, in parentheses, by the peak intensity relative to the base peak (100%) and where shown, the proposed signal assignment. All compounds submitted for mass spectral analysis were purified by either distillation or column chromatography and estimated to be at least 95% pure by NMR and thin layer chromatography.

7.1 The Synthesis of the Right Fragment

Ethyl (*S*)-*O*-(*tert*-butyldimethylsilyl)lactate.



3.4
$C_5H_{10}O_3$
Mol. Wt.: 118.13

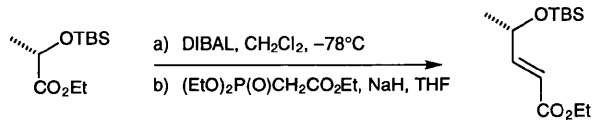
$C_{11}H_{24}O_3Si$
Mol. Wt.: 232.39

A solution of TBSCl (80 g, 530 mmol), ethyl (*S*)-lactate **3.4** (60.8 mL, 536 mmol), triethylamine (76.8 mL, 550 mmol) and DMAP (2.6 g, 21.2 mmol) in CH_2Cl_2 (400 mL) was heated at reflux for 24 h. The mixture was filtered through a pad of celite and washed with hexanes (2 x 100 mL). The filtrate was washed with 2M $HCl_{(aq)}$ (100 mL) and water (100 mL), dried (Na_2SO_4) and concentrated *in vacuo* at 30°C. The residue was vacuum distilled (98-100°C at 15 mm Hg) to give TBS ether (122 g, 525 mmol, 99 %) as a colourless liquid .

Observed $[\alpha]_D^{22}$ –30.0 (*c* 2.5, $CHCl_3$); lit. $[\alpha]_D$ –30.5 (*c* 2.1, $CHCl_3$)[111].

^1H and ^{13}C NMR spectra were in agreement with that reported in the literature[111].

Ethyl (*S*)-4-(*tert*-butyldimethylsilyloxy)pent-2-enoate 3.3.



$C_{11}H_{24}O_3Si$
Mol. Wt.: 232.39

3.3
$C_{13}H_{26}O_3Si$
Mol. Wt.: 258.43

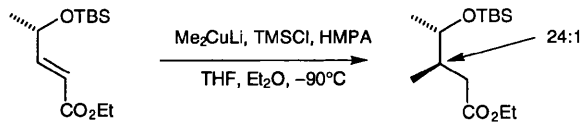
A solution of DIBAL (neat, 46 mL, 258 mmol) in CH_2Cl_2 (40 mL) was added dropwise to a stirred solution of TBS ethyl (*S*)-lactate (56.6 g, 244 mmol) in CH_2Cl_2 (640 mL) over 15 min at a rate sufficient to maintain a temperature between –78°C and –70°C. The reaction mixture was stirred at –78°C for 30 min before being quenched with acetone (6 mL) followed by saturated aqueous Na_2SO_4 (20 mL) and CH_2Cl_2 (400 mL). The mixture was stirred at ambient temperature for 1 h forming a milky suspension. Solid Na_2SO_4 (217 g) was added and the mixture stirred for a further 1 h. The mixture was filtered through a pad of Celite and the salt cake was washed with CH_2Cl_2 (3 x 70 mL). The filtrate was concentrated on the rotary evaporator at room temperature to give crude aldehyde (43.8 g) as a colourless liquid which was used immediately in the next step.

Triethyl phosphonoacetate (50 mL, 250 mmol) was added dropwise to a stirred suspension of sodium hydride (9.84 g, 60% dispersion in oil, 246 mmol, washed three times with hexanes) in THF (400 mL) between 0°C and –5°C over 20 min. The mixture was stirred for 15 min to form a homogeneous solution. A solution of crude aldehyde in THF (10 mL) was added dropwise over 35 min keeping the reaction temperature below 10°C. The cooling bath was removed and the reaction mixture was stirred at ambient temperature for 40 min. Acetone (20 mL, dried over K_2CO_3) was added and the mixture was stirred for a further 30 min before being quenched with saturated aqueous NH_4Cl (200 mL). The phases were separated and the aqueous phase was extracted with hexanes (2 x 300 mL). The combined organic extracts were washed with water (3 x 150 mL), brine (100 mL), dried (Na_2SO_4) and concentrated. The residue was distilled under reduced pressure and the fraction boiling between 102°C and 108°C at 0.2 mm Hg was collected to give enoate ester **3.3** (45.2 g, 77%) as a colourless oil.

^1H and ^{13}C NMR spectra were in agreement with that reported in the literature[65].

Ethyl (3*R*,4*S*)-4-(*tert*-butyldimethylsilyloxy)-3-methylpentanoate 3.2.

Ester **3.2** was synthesised according to literature procedure[64].



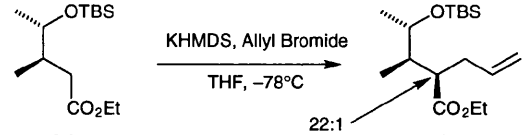
3.3
$C_{13}H_{26}O_3Si$
Mol. Wt.: 258.43

3.2
$C_{14}H_{30}O_3Si$
Mol. Wt.: 274.47

MeLi•LiBr complex (1.4 M in ether, 325 mL, 455 mmol) was added to a stirred suspension of CuI (43.3 g, 227.5 mmol) in THF (390 mL) between –10°C and 0°C over 30 min to form a cloudy grey solution. The mixture was cooled to –80°C whereupon HMPA (55.3 mL, 317.6 mmol) was added over 5 min. The mixture was further cooled to –95°C and a solution of enoate **3.3** (23.4 g, 95.0 mmol) and chlorotrimethylsilane (33.2 mL, 265.4 mmol) in THF (190 mL) was added dropwise between –95°C and –90°C over 40 min forming a green mixture. The reaction mixture was stirred at –95°C for 2 h. Saturated aqueous NH_4Cl (320 mL) was added carefully (gas evolution!) followed by water (300 mL) and concentrated aqueous ammonia (200 mL). The mixture was stirred at ambient temperature for 2 h. Hexanes (500 mL) were added and the phases separated. The aqueous layer was extracted with hexanes (2 x 150 mL) and the combined organic extracts were washed with brine (200 mL), dried (Na_2SO_4) and concentrated. The residue was treated with EtOH (75 mL) and water (3 mL) and stirred at 50°C for 45 min and then concentrated. The residue was purified by short path distillation to give ester **3.2** (18.6 g, 70.8 mmol, 75%) as a colourless oil: bp 66-72°C at 0.2 mm Hg. ^{13}C NMR spectroscopy ($CDCl_3$) revealed a 24:1 mixture of diastereoisomers according to integration of the signals at $\delta =$ 71.6 (major) and 70.7 (minor).

^1H and ^{13}C NMR spectra were in agreement with that reported in the literature[64].

Ethyl (2*R*,3*R*,4*S*)-2-allyl-4-(*tert*-butyldimethylsilyloxy)-3-methylpentanoate 3.5.



3.2
$C_{14}H_{30}O_3Si$
Mol. Wt.: 274.47

3.5
$C_{17}H_{34}O_3Si$
Mol. Wt.: 314.54

Ester **3.2** (24.0 g, 91.6 mmol) was added dropwise *via* syringe to a stirred solution of potassium bis(trimethylsilyl)amide (~80%, 23.3 g, 93.0 mmol) in THF (350 mL) at –78°C. The reaction mixture was stirred at –78°C for 30 min and then allyl bromide (40 mL, 456 mmol) was added dropwise. The reaction mixture was stirred at –78°C for 3 h, quenched with saturated aqueous NH_4Cl and extracted with hexanes (2 x 100 mL). The combined organic extracts were washed with brine (100 mL), dried (Na_2SO_4) and concentrated. The residue was purified by short path distillation to give ester **3.5** (22.2 g, 73.4 mmol, 80%) as a colourless oil:

bp 84-88°C at 0.5 mm Hg as a 22:1 mixture of diastereoisomers according to integration of the doublets at δ = 0.06 (minor) and 0.04 (major) as revealed in the ^{1}H NMR spectrum ($CDCl_3$).

$[\alpha]_D^{22}$ –2.9 (*c* 1.5, $CHCl_3$).

υ_{max} film/cm^{-1} 2926 (s), 1740(s), 1261 (m), 838 (s).

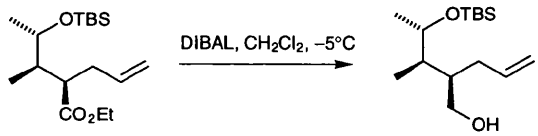
^{1}H NMR (360 MHz, $CDCl_3$): δ = 5.74 (1H, ddt, *J* = 17.0, 10.1, 7.0 Hz, =CH), 5.05 (1H, ddt, *J* = 17.1, 3.3, 1.5 Hz, =CH_AH_B), 4.99 (1H, dddd, *J* = 10.2, 3.0, 2.2, 1.1 Hz, =CH_AH_B), 4.21-4.04 (2H, m, OCH_2), 3.68 (1H, dq, *J* = 6.2, 5.4 Hz, C2-H), 2.47 (1H, ddd, *J* = 8.8, 7.6, 3.7 Hz, C4-H), 2.29 (2H, m, C5-H_2), 1.94-1.84 (1H, m, *J* = 7.0, 5.3 Hz, C3-H), 1.25 (3H, t, *J* = 7.1 Hz, OCH_2CH_3), 1.07 (3H, d, *J* = 6.2 Hz, C2-Me), 0.89 (3H, d, *J* = 7.0 Hz, C3-Me), 0.886 (9H, s, ^{t}BuSi), 0.043 and 0.036 (3H each, s, Me_2Si).

^{13}C NMR (90 MHz, $CDCl_3$): δ = 175.5 (0), 136.2 (1), 116.5 (2), 69.8 (1), 60.2 (2), 47.5 (1), 42.5 (1), 32.9 (2), 26.0 (3, 3C), 19.2 (3), 18.2 (0), 14.5 (3), 11.1 (3), –4.2 (3), –4.7 (3).

LRMS *m/z* (CI, NH_3) 315 [$(M+H)^+$, 6%], 332 [$(M+NH_4)^+$, 1], 275 (1.5), 202 (1.2), 110 (1.2).

HRMS (CI mode) Found: $(M+H)^+$, 315.2354. $C_{17}H_{35}O_3Si$ requires *M*, 315.2355.

(2*R*,3*R*,4*S*)-2-Allyl-4-*O*-(*tert*-butyldimethylsilyl)-3-methyl-1,4-pentandiol 3.9.



3.5
$C_{17}H_{34}O_3Si$
Mol. Wt.: 314.54

3.9
$C_{15}H_{32}O_2Si$
Mol. Wt.: 272.50

A solution of DIBAL (neat, 28 mL, 156 mmol) was added dropwise to a stirred solution of ester **3.5** (21.0 g, 66.9 mmol) in CH_2Cl_2 (30 mL) between 5°C and 10°C over 40 min. The reaction mixture was stirred at –5°C for 1 h. A mixture of water (4 mL) and acetone (40 mL) was added dropwise over 45 min. keeping the temperature of the reaction mixture below 20°C. The clear solution became a white solid. Aqueous 2M $HCl_{(aq)}$ (230 mL) was then added over 15 min. The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 100 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. Kugelrohr distillation afforded alcohol **3.9** (16.2 g, 59.6 mmol, 89%) as a colourless oil: bp 140-145°C at 0.02 mm Hg.

$[\alpha]_D^{22}$ +1.1 (*c* 1.6, $CHCl_3$).

υ_{max} film/cm^{-1} 3374 (br), 1261 (s), 838 (s).

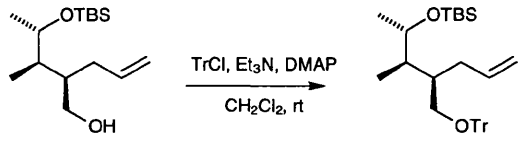
^{1}H NMR (360 MHz, $CDCl_3$): δ = 5.84 (1H, dddd, J = 17.1, 10.1, 7.8, 5.8 Hz, =CH), 5.06 (1H, dm, J = 17.1 Hz, =CH_AH_B), 5.01 (1H, dm, J = 10.0 Hz, =CH_AH_B), 3.78 (1H, dq, J = 6.2 Hz, C2-H), 3.68 (1H, dd, J = 11.0, 4.4 Hz, CH_AH_BOH), 3.49 (1H, dd, J = 11.0, 6.3 Hz, CH_AH_BOH), 2.30-2.10 (1H, m), 1.95-1.50 (4H, m), 1.16 (3H, d, J = 6.2 Hz, C2-Me), 0.90 (9H, s, ^{t}BuSi), 0.85 (3H, d, J = 7.0 Hz, C3-Me), 0.08 and 0.06 (3H each, s, Me_2Si).

^{13}C NMR (90 MHz, $CDCl_3$): δ = 138.3 (1), 116.1 (2), 71.0 (1), 64.1 (2), 41.1 (1), 40.8 (1), 32.6 (2), 26.1 (3, 3C), 21.5 (3), 18.2 (0), 12.5 (3), –4.0 (3), –4.7 (3).

LRMS m/z (CI, NH_3) 273 [$(M+H)^+$, 100%], 290 [$(M+NH_4)^+$, 50]

HRMS (CI mode) Found: $(M+H)^+$, 273.2247. $C_{15}H_{33}O_2Si$ requires M, 273.2250

(2*R*,3*R*,4*S*)-2-Allyl-4-*O*-(*tert*-butyldimethylsilyl)-3-methyl-1-*O*-triphenylmethyl-1,4-pentandiol 3.10.



3.9
$C_{15}H_{32}O_2Si$
Mol. Wt.: 272.50

3.10
$C_{34}H_{46}O_2Si$
Mol. Wt.: 514.81

A solution of alcohol **3.9** (15.0 g, 55.0 mmol), trityl chloride (17.3 g, 62.0 mmol), triethylamine (22 mL, 157 mmol) and DMAP (610 mg, 5.0 mmol) was stirred at room temperature for 12 h. The mixture was then poured onto aqueous saturated $NaHCO_3$ and extracted with CH_2Cl_2 (3 x 100 mL) and concentrated. The oily residue was dissolved in Et_2O (100 mL) treated with hexanes (200 mL) and washed with water (500 mL). The organic layer was dried (Na_2SO_4) and concentrated. The residue was filtered through a pad of silica gel (75 g, hexanes:Et_2O 5%) to give trityl ether **3.10** (26.6 g, 51.7 mmol, 94%) as a colourless oil : $[\alpha]_D^{22}$ +9.8 (c 1.0, $CHCl_3$).

υ_{max} film/cm^{-1} 2935 (m), 1452 (m), 829 (s).

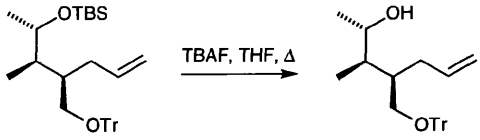
^{1}H NMR (360 MHz, $CDCl_3$): δ = 7.50-7.15 (15H, m), 5.65 (1H, dddd, J = 17.1, 10.1, 7.8, 5.8 Hz, =CH), 4.95-4.82 (2H, m, =CH_2), 3.73 (1H, dq, J = 6.2 Hz, C2-H), 3.10 (1H, dd, J = 9.2, 4.8 Hz, CH_AH_BO), 2.90 (1H, dd, J = 9.0, 7.6 Hz, CH_AH_BO), 2.30-2.20 (1H, m), 2.13-2.03 (1H, m), 1.89-1.76 (2H, m), 1.09 (3H, d, J = 6.1 Hz, C2-Me), 0.91 (9H, s, ^{t}BuSi), 0.72 (3H, d, J = 7.1 Hz, C3-Me), 0.04 and 0.02 (3H each, s, Me_2Si).

^{13}C NMR (90 MHz, $CDCl_3$): δ = 144.7 (0, 2C), 144.7 (0), 137.9 (1), 129.0 (1, 3C), 128.8 (1, 2C), 127.9 (1, 3C), 127.8 (1, 2C), 127.0 (1, 3C), 126.9 (1, 2C), 115.6 (2), 86.6 (0), 70.6 (1), 64.6 (2), 41.0 (1), 38.8 (1), 31.8 (2), 26.1 (3, 3C), 21.0 (3), 18.2 (0), 11.2 (3), –3.8 (3), –4.7 (3).

LRMS m/z (CI, NH_3) 532 [$(M+NH_4)^+$, 7%], 243 (100).

HRMS (CI mode) Found: $(M+NH_4)^+$, 532.3610. $C_{34}H_{50}O_2NSi$ requires *M*, 532.3611.

(2*R*,3*R*,4*S*)-2-Allyl-3-methyl-1-*O*-triphenylmethyl-1,4-pentandiol 3.11.



3.10
$C_{34}H_{46}O_2Si$
Mol. Wt.: 514.81

3.11
$C_{28}H_{32}O_2$
Mol. Wt.: 400.55

A solution of TBS ether **3.10** (53.6 g, 104.0 mmol) and TBAF trihydrate (53.0 g, 168.0 mmol) in THF (200 mL) was stirred at reflux for 5 h. After cooling to room temperature, the mixture was poured onto water (1 L) and extracted with Et_2O (3 x 150 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated to give crude alcohol **3.11** (40.4 g, 100.9 mmol, 97%) as a colourless oil which was immediately used in the next step. For analysis a sample purified by column chromatography (SiO_2, haxanes:Et_2O 5-10%) gave: $[\alpha]_D^{22}$ +12.3 (*c* 1.6, $CHCl_3$).

υ_{max} film/cm^{-1} 3409 (br), 1449 (s), 706 (s).

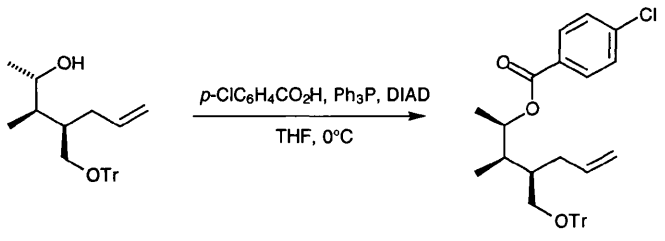
^1H NMR (360 MHz, $CDCl_3$): δ= 7.50-7.15 (15H, m), 5.71 (1H, ddt, *J* = 17.1, 10.1, 7.2 Hz, =CH), 4.96 (1H, dm, *J* = 17.2 Hz, $=CH_AH_B$), 4.91 (1H, dm, *J* = 10.1 Hz, $=CH_AH_B$), 3.61 (1H, quintet, *J* = 6.7 Hz, C2-H), 3.15 (1H, dd, *J* = 9.3, 4.8 Hz, CH_AH_BO), 3.00 (1H, dd, *J* = 9.3, 7.1 Hz, CH_AH_BO), 2.30-2.28 (1H, m), 2.10-1.87 (2H, m), 1.78 (1H, ddq, *J* = 7.1, 4.1 Hz, C3-H), 1.68 (1H, br, OH), 1.11 (3H, d, *J* = 6.2 Hz, C2-Me), 0.67 (3H, d, *J* = 7.0 Hz, C3-Me).

^{13}C NMR (90 MHz, $CDCl_3$): δ= 144.4 (0, 3C), 137.9 (1), 128.8 (1, 4C), 127.8 (1, 8C), 126.9 (1, 3C), 115.8 (2), 86.7 (0), 69.6 (1), 64.3 (2), 41.1 (1), 39.4 (1), 32.0 (2), 21.0 (3), 11.6 (3).

LRMS *m/z* (CI, NH_3) 418 $[(M+NH_4)^+$, 0.4%], 243 (32).

Microanalysis: Anal. Calcd for $C_{28}H_{32}O_2$: C, 84.00; H, 8.00. Found: C, 84.07; H, 8.00.

(2*R*,3*R*,4*R*)-2-Allyl-4-*O*-(4-chlorobenzoyl)-3-methyl-1-*O*-triphenylmethyl-1,4-pentanediol 3.1.



3.11
$C_{28}H_{32}O_2$
Mol. Wt.: 400.55

3.1
$C_{35}H_{35}ClO_3$
Mol. Wt.: 539.10

A solution of DIAD (16.05 mL, 81.5 mmol) in THF (10 mL) was added dropwise to a stirred solution of crude alcohol **3.11** (18.5 g, 46.3 mmol) as prepared in the previous step, triphenylphosphine (21.4 g, 81.6 mmol) and *p*-chlorobenzoic acid (12.8 g, 81.7 mmol) in THF (150 mL). During addition the temperature was maintained between –7°C and 0°C. The reaction mixture was stirred for 3 h between –10°C and 0°C. Water (1 mL) was added and the mixture was stirred at ambient temperature for 15 min then concentrated. The residual oil was treated with Et_2O (50 mL) and hexanes (100 mL) were added dropwise to cause formation of white crystals. The crystals were filtered off and washed with hexanes (3 x 50 mL). The filtrate was extracted with 2M $NaOH_{(aq)}$ (2 x 30 mL), water (50 mL) and brine (50 mL), dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography (SiO_2 150 g, hexanes:ether 0-4%) to give ester **3.1** (19.0 g, 35.2 mmol, 76%) as a colourless oil which solidified on standing in the refrigerator to give a white solid: mp 102-102.5 °C (MeOH:H_2O).

$[\alpha]_D^{22}$ –25.7 (*c* 1.25, $CHCl_3$).

υ_{max} film/cm^{-1} 2972 (m), 1719 (s), 1273 (s), 762 (s).

^1H NMR (360 MHz, $CDCl_3$): δ = 7.91 (2H, dm, *J* = 8.6 Hz), 7.50-7.35 (7H, m), 7.30-7.15 (10H, m), 5.63 (1H, ddt, *J* = 17.1, 10.1, 7.0 Hz, =CH), 5.09 (1H, dq *J* = 6.3 Hz, C2-H), 4.92 (1H, dm, *J* = 17.1 Hz, $=CH_AH_B$), 4.90 (1H, dm, *J* = 10.1 Hz, $=CH_AH_B$), 3.11 (1H, 4 lines of ABX system, *J* = 9.4, 7.2 Hz, CH_AH_BO), 3.08 (1H, 4 lines of ABX system, *J* = 9.4, 5.7 Hz, CH_AH_BO), 2.25-2.12 (1H, m), 2.10-1.95 (2H, m), 1.90-1.80 (1H, m), 1.32 (3H, d, *J* = 6.3 Hz, C2-Me), 0.92 (3H, d, *J* = 7.0 Hz, C3-Me).

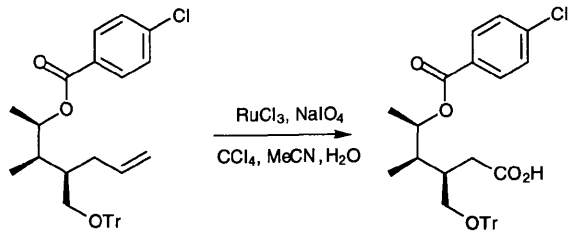
^{13}C NMR (90 MHz, $CDCl_3$): δ = 165.2 (0), 144.4 (0, 3C), 139.3 (0), 137.1 (1), 131.1 (1, 2C), 129.9 (0, 3C), 128.9 (1, 3C), 128.8 (1, 3C), 127.9 (1, 6C), 127.0 (1, 3C), 116.3 (2), 86.7 (0), 73.8 (1), 63.6 (2), 41.0 (1), 38.1 (1), 32.2 (2), 18.7 (3), 11.1 (3).

LRMS *m/z* (CI, NH_3) 556 [$(M+NH_4)^+$, 0.24], 539 [$(M+H)^+$, 0.01%], 316 (4), 263 (2), 243 (100).

Microanalysis: Anal. Calcd for $C_{35}H_{35}ClO_3$: C, 77.99; H, 6.49. Found: C, 77.92; H, 6.60.

(3*R*,4*R*,5*R*)-5-(4-Chlorobenzoyloxy)-4-methyl-3-(triphenylmethoxymethyl) hexanoic acid 3.13.

Cleavage of an olefin and oxidation to a carboxylic acid is described in the literature[73].



3.1
$C_{35}H_{35}ClO_3$
Mol. Wt.: 539.10

3.13
$C_{34}H_{33}ClO_5$
Mol. Wt.: 557.08

Sodium metaperiodate (11.1 g, 51.9 mmol) was added to a stirred mixture of olefin **3.1** (6.4 g, 11.9 mmol), CCl_4 (60 mL), acetonitrile (60 mL) and water (50 mL). After 15 min $RuCl_3 \cdot 3H_2O$ (190 mg, 0.75 mmol) was added and the reaction mixture was stirred vigorously for 5 h. The mixture was poured onto water (300 mL) the organic layer removed and the aqueous phase extracted with CH_2Cl_2 (3 x 50 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography (SiO_2 100 g, hexanes:Et_2O 20-40%) to give acid **3.13** (3.47 g, 6.25 mmol, 53%) as a white foam: mp 55-58°C.

$[\alpha]_D^{22}$ –44.4 (*c* 0.9, $CHCl_3$).

υ_{max} KBr/cm^{-1} 3422 (br), 1716 (s), 1273 (s).

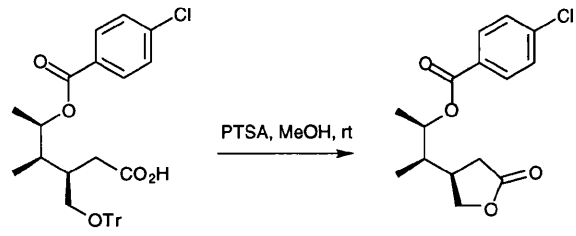
^{1}H NMR (360 MHz, $CDCl_3$): δ = 7.87 (2H, dm, *J* = 7.2 Hz), 7.48-7.5 (7H, m), 7.32-7.15 (10H, m), 5.09 (1H, dq, *J* = 6.0, 0.9 Hz, C2-H), 3.24 (1H, dm, *J* = 4.4 Hz), 3.09 (1H, dm, *J* = 6.2 Hz), 2.49-2.32 (3H, m), 2.04-1.94 (1H, m), 1.33 (3H, d, *J* = 6.3 Hz, C2-Me), 0.94 (3H, d, *J* = 7.0 Hz, C3-Me).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 179.5 (0), 165.1 (0), 144.1 (0, 3C), 139.4 (0), 131.1 (1, 3C), 129.2 (0), 128.8 (1, 3C), 128.8 (1, 3C), 128.8 (1, 3C), 127.9 (1, 5C), 127.1 (1, 2C), 86.9 (0), 73.2 (1), 64.3 (2), 38.4 (1), 37.9 (1), 33.8 (2), 18.4 (3), 11.3 (3).

LRMS *m/z* (EI$^+$) 556 [(M+H)$^+$, 0.03%], 479 (0.15), 400 (3), 324 (7), 243 (100), 165 (46), 139 (70).

HRMS (FAB mode) Found: (M+Na)$^+$, 579.1913. $C_{34}H_{33}O_5ClNa$ requires *M*, 579.1914.

(4*R*)-4-[(1*R*,2*R*)-2-(4-Chlorobenzoyloxy)-1-methylpropyl]-dihydrofuran-2(3*H*)-one 3.14.



3.13
$C_{34}H_{33}ClO_5$
Mol. Wt.: 557.08

3.14
$C_{15}H_{17}ClO_4$
Mol. Wt.: 296.75

A solution of acid **3.13** (3.47 g, 6.25 mmol) and *p*-toluenesulfonic acid (160 mg, 0.84 mmol) in MeOH (60 mL) was stirred at room temperature for 3 h before being concentrated. The residue was purified by column chromatography (SiO_2 30 g, hexanes:Et_2O 10-50%) to give lactone **3.14** (1.32 g, 4.45 mmol, 71%) as a white solid. All minor diastereomeric impurities were removed by recrystallisation from hexanes:Et_2O to give pure lactone **3.14** (1.08g, 3.63 mmol, 58%) as colourless rock crystals: mp 69.5-70°C (hexanes:Et_2O).

$[\alpha]_D^{22}$ –0.4 (*c* 1.9, $CHCl_3$).

υ_{max} film/cm^{-1} = 1785 (s), 1716 (s), 1595 (m), 1275 (s).

^1H NMR (360 MHz, $CDCl_3$): δ = 7.93 (2H, dd, *J* = 6.7, 2.0 Hz), 7.43 (2H, dd, *J* = 6.8, 2.0 Hz), 5.17 (1H, dq *J* = 6.5, 2.7 Hz, C2-H), 4.55 (1H, dd, *J* = 9.0, 8.1 Hz, CH_AH_BO), 4.03 (1H, t, *J* = 9.1 Hz, CH_AH_BO), 2.67-2.52 (2H, m), 2.33-2.21 (1H, m), 1.90-1.80 (1H, m), 1.34 (3H, d, *J* = 6.5 Hz, C2-Me), 1.10 (3H, d, *J* = 6.9 Hz, C3-Me).

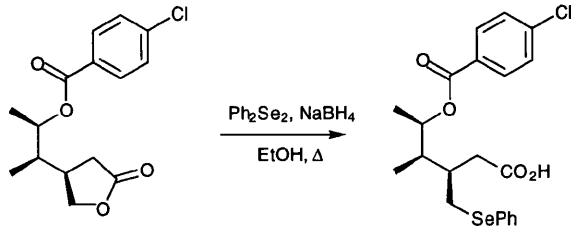
^{13}C NMR (90 MHz, $CDCl_3$): δ = 176.4 (0), 165.0 (0), 139.7 (0), 130.9 (1, 2C), 128.9 (1, 2C), 128.6 (0), 72.6 (1), 72.4 (2), 41.0 (1), 38.5 (1), 33.0 (2), 16.7 (3), 13.0 (3).

LRMS *m/z* (CI, *Iso*butane) 297 [$(M+H)^+$, 5%], 265 (1.7), 139 (100), 111 (20), 82 (12).

Microanalysis: Anal. Calcd for $C_{15}H_{17}ClO_4$: C, 60.71; H, 5.73. Found: C, 60.84; H, 5.74.

(3*S*,4*R*,5*R*)-5-(4-Chlorobenzoyloxy)-4-methyl-3-(phenylselenylmethyl) hexanoic acid 3.15.

Alkoxy bond cleavage of six membered lactones using Ph_2Se_2, $NaBH_4$ and 18-crown-6 is described in the literature[74].



3.14
$C_{15}H_{17}ClO_4$
Mol. Wt.: 296.75

3.15
$C_{21}H_{23}ClO_4Se$
Mol. Wt.: 453.82

Sodium borohydride (348 mg) was added in several portions to a stirred yellow suspension of diphenyl diselenide (1.6 g, 5.15 mmol) in anhydrous EtOH (5.8 mL) to cause exothermic reaction and gas evolution. Lactone **3.14** (991 mg, 3.34 mmol) was then added to the pale yellow homogeneous solution of sodium phenylselenide. The resulting mixture was stirred at reflux for 11 h. After cooling to room temperature the reaction mixture was diluted with Et_2O (8 mL) and treated with 2M $HCl_{(aq)}$ (5 mL). The layers were separated and the aqueous phase was extracted with Et_2O (3 x 20 mL). The combined organic extracts were washed with diluted aqueous $NaHCO_3$ (2 x 10 mL), dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography (SiO_2 20 g, hexanes:Et_2O 10-30%) to give acid **3.15** (1.33 g, 2.93 mmol, 88%) as a yellow oil.

$[\alpha]_D^{22}$ –3.5 (*c* 1.5, $CHCl_3$).

υ_{max} film/cm^{-1} 1719 (s), 1595 (s), 1281 (s), 1100 (s).

^1H NMR (360 MHz, $CDCl_3$): δ = 7.97-7.90 (2H, dm, *J* = 8.5), 7.50-7.45 (2H, m), 7.44-7.38 (2H, dm, *J* = 8.5), 7.23-7.16 (3H, m), 5.18 (1H, quintet, *J* = 6.2, Hz, C2-H), 3.06 (1H, dd, *J* = 5.8, 3.0 Hz, C-5 H_AH_B), 3.02 (1H, dd, *J* = 5.6, 3.0 Hz, C-5H_AH_B), 2.61 (1H, dd, *J* = 11.5, 4.9 Hz, CH_AH_BSe), 2.48 (1H, dd, *J* = 16.4, 8.0 Hz, CH_AH_BSe), 2.34-2.24 (1H, m, C4-H), 2.15-2.05 (1H, m, ,C3-H), 1.28 (3H, d, *J* = 6.3 Hz, C2-Me),1.01 (3H, d, *J* = 7.0 Hz, C3-Me).

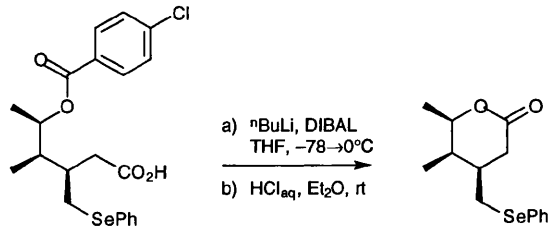
^{13}C NMR (90 MHz, $CDCl_3$): δ = 179.2 (0), 165.3 (0), 139.5 (0), 133.0 (1), 131.1 (1, 2C), 129.8 (0), 129.2 (1, 2C), 129.0 (0), 128.8 (1, 2C), 127.2 (1, 2C), 73.2 (1), 40.0 (1), 37.2 (1), 35.5 (2), 31.5 (2), 18.5 (3), 10.8 (3).

LRMS *m/z* (EI^+) 454 [$(M+H)^+$, 8%], 298 (24), 156 (45), 139 (100), 111 (29).

Microanalysis: Anal. Calcd for $C_{21}H_{23}ClO_4Se$: C, 55.56; H, 5.07. Found: C, 55.53; H, 5.23.

(2*R*,3*R*,4*R*)-5,6-Dimethyl-4-phenylselenylmethyl-tetrahydro-2*H*-pyran-2-one 3.17.

The reduction of an ester using an 'ate' complex is described in the literature.[75,112]



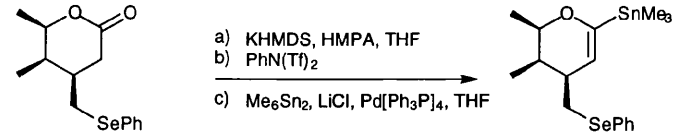
3.15
$C_{21}H_{23}ClO_4Se$
Mol. Wt.: 453.82

3.17
$C_{14}H_{18}O_2Se$
Mol. Wt.: 297.25

^{n}BuLi (2.32 M in hexanes, 3.75 mL, 8.7 mmol) was added dropwise to a solution of DIBAL (neat, 1.55 mL, 8.7 mmol) in CH_2Cl_2 (16 mL) at –5°C. THF (32 mL) was then added. The mixture was cooled to –78°C and ester **3.15** (1.31 g, 2.90 mmol) in THF (24 mL + 8 mL) was added *via* cannula. The mixture was left to warm to –20°C over 2 min. and stirred at –20°C for 3 h. The mixture was then treated with 2M $HCl_{(aq)}$ (50 mL, 30 eq), and Et_2O (50 mL) and stirred vigorously for 24 h. The organic layer was removed and the aqueous phase extracted with Et_2O (2 x 40 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography (SiO_2 40 g, hexanes:ether 10-30%) to give lactone **3.17** (619 mg, 2.08 mmol, 72%) as a clear colourless oil.

^1H and ^{13}C NMR spectra were in agreement with that reported in the literature[36].

(2*R*3*R*,4*R*)-3,4-Dihydro-2,3-dimethyl-4-phenylselenylmethyl-6-trimethylstannyl-2*H*-pyran 1.72.



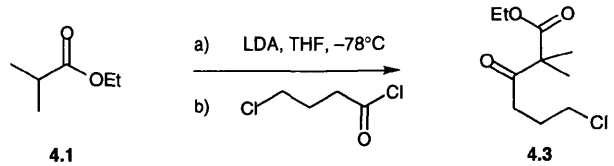
3.17
$C_{14}H_{18}O_2Se$
Mol. Wt.: 297.25

1.72
$C_{17}H_{26}OSeSn$
Mol. Wt.: 444.06

As previously reported in the literature with 70% yield[36].

7.2 The Synthesis of 18-*O*-Methyl Mycalamide B.

Ethyl -6-chloro-3-carbonyl-2,2-dimethylhexanoate 4.3.



4.1
$C_6H_{12}O_2$
Mol. Wt.: 116.16

4.3
$C_{10}H_{17}ClO_3$
Mol. Wt.: 220.69

^{n}BuLi (2.5 M in THF, 120 mL, 0.30 moles) was added dropwise to a solution of diisopropylamine (42.0 mL, 0.30 moles) in THF (100 mL) at 0°C over 15 min. After 1 h at 0°C the mixture was cooled to –78°C to which a solution of ethyl isobutyrate **4.1** (40.1 mL, 0.30 moles) in THF (100 mL) was added over 30 min keeping the temperature of the reaction mixture below –70°C. After 1 h a solution of 4-chlorobutyryl chloride **4.2** (33.6 mL, 0.30 moles) in THF (50 mL) was added over 20 min keeping the temperature of the reaction mixture below –68°C. The mixture was left to stir for 1 h at –78°C before the reaction was quenched by the addition of aqueous saturated NH_4Cl (200 mL). The organic phase was removed and washed successively with H_2O (3 x 200 mL) and brine before being dried ($MgSO_4$) and concentrated. The orange residue was filtered through a pad of silica eluting with hexanes:Et_2O (5:1), concentrated and purified by short path distillation (ob 110°C, head 78-84°C at 0.1 mm Hg) to return β-keto ester **4.3** (61.6 g, 280 mmol, 93%) as a pale yellow oil.

ν_{max} film/cm^{-1} 1714 (s).

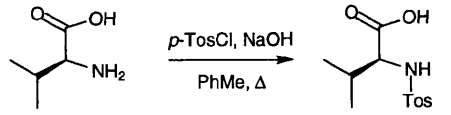
^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.19 (2H, q, J = 7.1 Hz, CH_3CH_2O), 3.56 (2H, t, J = 6.0 Hz, C18-H_2), 2.66 (2H, t, J = 6.8 Hz, C16-H_2), 2.06 (2H, dt, J = 6.6, 6.8 Hz, C17-H_2), 1.37 (6H, s, C14-Me_2), 1.26 (3H, t, J = 7.1 Hz, CH_3CH_2O).

^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 207.3 (0), 173.7 (0), 61.6 (2), 55.7 (0), 44.4 (2), 34.8 (2), 26.7 (2), 22.0 (3, 2C), 14.2 (3).

LRMS *m/z* (CI) 221 [$(M+H)^+$, 100%], 185 (45).

HRMS (CI) Found: $(M+H)^+$, 221.0946. $C_{10}H_{18}ClO_3$ requires M, 221.0944.

(*S*)-*N*-(4-Methylbenzenesulfonyl)valine 4.9.



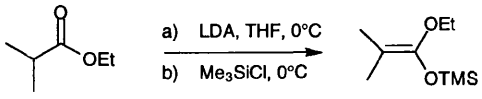
4.8
$C_5H_{11}NO_2$
Mol. Wt.: 117.15

4.9
$C_{12}H_{17}NO_4S$
Mol. Wt.: 271.33

4.9 Was synthesised according to literature procedure[113] in 72% yield.
Observed mp 147-148°C; literature mp 147°C[114].

1-Ethoxy-2-methyl-1-(trimethylsilyloxy)-1-propene 4.6.

Enol silane **4.6** was synthesised according to literature procedure[115].



4.1
$C_6H_{12}O_2$
Mol. Wt.: 116.16

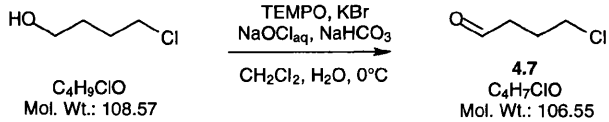
4.6
$C_9H_{20}O_2Si$
Mol. Wt.: 188.34

^{n}BuLi (2.37 M in hexanes, 192 mL, 455 mmol) was added to a mechanically stirred solution of diisopropylamine (67 mL, 473 mmol) in THF (350 mL) at 0°C over 30 min. After stirring at 0°C for 20 min ethyl isobutyrate (60 mL, 450 mmol) was added over 10 min maintaining a temperature of 0°C. After a further 30 min chlorotrimethylsilane (140 mL) was added at 0°C over 15 min. After 10 min the cooling bath was removed and the reaction mixture was stirred at room temperature for 1 h. After such time the mixture was filtered (under N_2) and concentrated *in vacuo* using a 50 cm Vigreux distillation column. The residue was filtered again (under N_2) and purified by short path distillation to give enol silane **4.6** (81 g, 430 mmol, 95%) as a clear colourless oil: bp 80-90°C at 10.0 mm Hg.

^{1}H NMR spectroscopic data was in agreement with literature[115].

4-Chlorobutanal 4.7.

The TEMPO oxidation was performed according to a literature procedure[116].



C_4H_9ClO
Mol. Wt.: 108.57

4.7
C_4H_7ClO
Mol. Wt.: 106.55

A mixture of 4-chlorobutanol (50 mL, 475-450 mmol), TEMPO (780 mg, 5 mmol), CH_2Cl_2 (170 mL) and a solution of KBr (6 g, 50 mmol) in water (25 mL) was vigorously stirred and cooled to –10°C. A pre-cooled solution of sodium hypochlorite (272 mL, 13%), $NaHCO_3$ (9.34 g) and water (280 mL) was added over 20 min

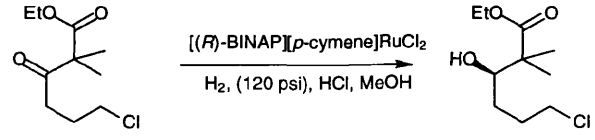
keeping the temperature of the reaction mixture between 5°C and 10°C. The reaction mixture was stirred for 15 min and then the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (50 mL) and the combined organic extracts were washed successively with 2M $HCl_{(aq)}$ (100 mL) containing KI (3 g), 10% aqueous $Na_2S_2O_3$ (100 mL) and 5% aqueous $NaHCO_3$. The organic phase was dried (Na_2SO_4) and concentrated *in vacuo* at room temperature. The residue was purified by short path distillation to give aldehyde **4.7** (34.2 g, 318-321.0 mmol, 67-71%) as a clear colourless oil: bp 62-65°C at 10.0 mm Hg.

^1H NMR spectroscopic data was in agreement with literature[117].

Ethyl (*R*)-6-chloro-3-hydroxy-2,2-dimethylhexanoate 4.4.

Method 1: Reduction of β-keto ester 4.3.

The enantioselective reduction of β-keto esters without the *gem*-dimethyl group is described in the literature [81].

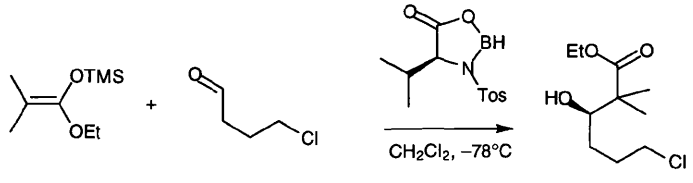


4.3
$C_{10}H_{17}ClO_3$
Mol. Wt.: 220.69

4.4
$C_{10}H_{19}ClO_3$
Mol. Wt.: 222.71

A Parr high pressure hydrogenator was charged with a solution of the β–ketoester **4.3** (11.0 g, 50.0 mmol) in methanol (100 mL). Methanolic HCl (2M, 0.1 mL) was added followed by [(*R*)-BINAP][*p*-cymene]$RuCl_2$ (0.2 mol %, 93 mg). The apparatus was evacuated and filled with hydrogen three times and the mixture allowed to stir at 120 psi and 40°C for three days under an atmosphere of hydrogen. After such time the mixture was concentrated *in vacuo* and the residue purified by filtration through a pad of silica (30 g) eluting with hexanes:Et_2O (5:1). Hydroxy ester **4.4** (10.4 g, 46.7 mmol, 93%) was obtained as a pale yellow oil. ^1H NMR integration of the C14-Me singlets from the derived (*R*)-MTPA ester determined enantiomeric ratio of hydroxy ester as 97:3 [(270 MHz, C_6D_6, referenced to 7.16 ppm): δ= 1.16 (major), 1.11 (minor)].

Method 2: Mukiyama Directed Aldol Reaction



4.6
$C_9H_{20}O_2Si$
Mol. Wt.: 188.34

4.7
C_4H_7ClO
Mol. Wt.: 106.55

4.4
$C_{10}H_{19}ClO_3$
Mol. Wt.: 222.71

A solution of BH_3•THF complex (1 M in THF, 10 mL, 10 mmol) was added dropwise to a stirred suspension of (*S*)-*N*-tosylvaline **4.9** (2.71 g, 10 mmol) in CH_2Cl_2 (50 mL) at room temperature over 25 min. After 10 min the

reaction mixture was cooled to –78°C and aldehyde **4.7** (1.06 g, 10 mmol) was added followed by silyl ketene acetal **4.6** (2.03 g, 10.8 mmol). After 1.5 h at –78°C the reaction mixture was quenched with saturated aqueous $NaHCO_3$, diluted with hexanes (100 mL) and washed with water (3 x 50 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography (SiO_2 30 g, hexanes:AcOEt 0-20%) to give hydroxy ester **4.4** (1.74 g, 7.8 mmol, 78%) as a colourless oil. ^1H NMR integration of the C14-Me singlets from the derived (*R*)-MTPA ester determined enantiomeric ratio of hydroxy ester as 97:3 [(270 MHz, C_6D_6, referenced to 7.16 ppm): δ= 1.16 (major), 1.11 (minor)].

$[\alpha]_D^{27}$ +18.7 (*c* 0.9, $CHCl_3$).

ν_{max} film/cm^{-1} 3490 (br), 1718 (s).

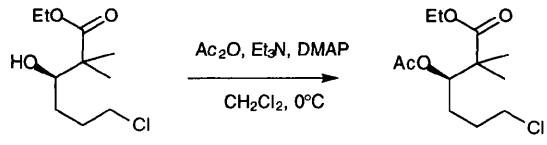
^1H NMR (360 MHz, $CDCl_3$): δ = 4.13 (2H, q, *J* = 7.1 Hz, CH_3CH_2O), 3.64-3.50 (3H, m, C15-H and C18-H_2), 2.75 (1H, br s, OH), 2.15-2.00 (1H, m, C17-H), 1.82 (1H, ddq, *J* = 14.5, 9.2, 6.2 Hz, C17-H), 1.65 (1H, dddd, *J* = 13.5, 9.3, 6.0, 1.9 Hz, C16-H_AH_B), 1.35 (1H, dddd, *J* = 13.9, 10.8, 9.3, 4.8 Hz, C16-H_AH_B), 1.24 (3H, t, *J* = 7.1 Hz, CH_3CH_2O), 1.17 (3H, s, C14-Me), 1.15 (3H, s, C14-Me).

^{13}C NMR (90 MHz, $CDCl_3$): δ = 177.8 (0), 76.1 (1), 60.9 (2), 47.1 (0), 45.2 (2), 29.8 (2), 28.9 (2), 22.4 (3), 20.4 (3), 14.2 (3).

LRMS *m/z* (CI, NH_3) 223 [$(M+H)^+$, 100%], 205 (25), 187 (45), 116 (20).

Microanalysis: Anal. Calcd for $C_{10}H_{19}O_3Cl$: C, 53.93; H, 8.54. Found: C, 53.67; H, 8.29.

Ethyl (*R*)-3-acetoxy-6-chloro-2,2-dimethylhexanoate 4.11.

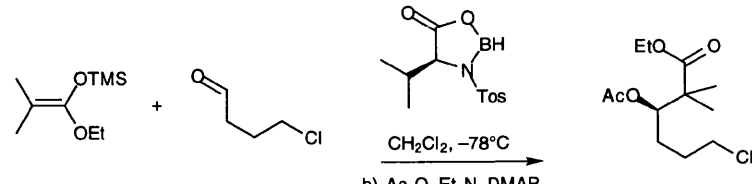


4.4
$C_{10}H_{19}ClO_3$
Mol. Wt.: 222.71

4.11
$C_{12}H_{21}ClO_4$
Mol. Wt.: 264.75

An ice cold solution of the β-hydroxyester **4.4** (20.7 g, 93. 0 mmol) in CH_2Cl_2 (160 mL) was treated with triethylamine (11.3 g, 15.6 mL, 112.0 mmol), acetic anhydride (11.4 g, 10.5 mL, 112.0 mmol) and DMAP (40 mg). After 5 min the ice bath was removed and the mixture was left to warm up to room temperature. After stirring overnight at room temperature the mixture was diluted with hexanes (400 mL), washed with water (3 x 100 mL), brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by short path vacuum distillation to give the acetate ester **4.11** (20.1 g, 76.0 mmol, 82%) as a pale yellow oil: bp 86-92°C at 0.1 mm Hg.

Aldol reaction followed by acetate formation.



4.6
$C_9H_{20}O_2Si$
Mol. Wt.: 188.34

4.7
C_4H_7ClO
Mol. Wt.: 106.55

4.11
$C_{12}H_{21}ClO_4$
Mol. Wt.: 264.75

A solution of BH_3•THF complex (1 M in THF, 153 mL, 153 mmol) was added dropwise to a stirred suspension of (*S*)-*N*-tosylvaline **4.9** (41.9 g, 154 mmol) in CH_2Cl_2 (780 mL) at 25°C over 1 h. After 30 min the clear solution was cooled to –74°C and a solution of aldehyde **4.7** (16.3 g, 153.3 mmol) in CH_2Cl_2 (10 + 5 mL) was added over 5 min. Then silyl ketene acetal **4.6** (31.7 g, 169 mmol) was added over 10 min at a rate sufficient to maintain the temperature of the reaction mixture below –68°C. After 2 h at –74°C the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (250 mL), warmed up to room temperature and stirred vigorously for 30 min before being treated with water (250 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (50 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was diluted with hexanes (300 mL) and washed with aqueous $NaHCO_3$. The organic phase was dried (Na_2SO_4) and concentrated to a pale yellow oil (32 g) which was used immediately in the next step.

An ice cooled solution of the crude product from above (32 g) in CH_2Cl_2 (100 mL) was treated with triethylamine (25 mL, 180 mmol), acetic anhydride (16 mL, 168 mmol) and DMAP (76 mg, 0.6 mmol). After 5 min the ice bath was removed and the reaction mixture was stirred at room temperature for 3 h. The mixture was diluted with hexanes (300 mL), washed with water (3 x 100 mL), brine (50 mL), dried (Na_2SO_4) and concentrated. The residue was filtered through a pad of silica (15 g, hexanes:Et_2O) and purified by short path vacuum distillation (88-98°C at 0.1 mm Hg) to give acetate **4.11** (30 g, 113 mmol, 74% over 2 steps) as a clear colourless oil: bp 88-98°C at 0.1 mm Hg.

$[\alpha]_D^{22}$ + 9.4 (*c* 1.6, $CHCl_3$).

ν_{max} film/cm^{-1} 1718 (s), 1236 (s).

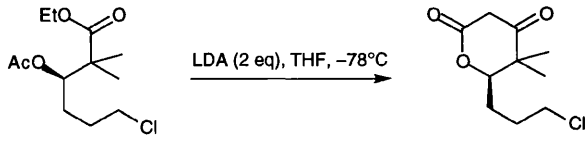
^1H NMR (270 MHz, $CDCl_3$): δ = 5.24 (1H, dd, *J* = 9.3, 3.9 Hz, C15-H), 4.14 (2H, q, *J* = 7.1 Hz, CH_2O), 3.63-3.49 (2H, m, C18-H_2), 2.06 (3H, s, C12-H_3), 1.83-1.57 (4H, m, C16-H_2 and C17-H_2), 1.26 (3H, t, *J* = 7.1 Hz, CH_3CH_2O), 1.18 (6H, s, C14-Me).

^{13}C NMR (90 MHz, $CDCl_3$): δ = 175.6 (0), 170.7 (0), 76.2 (1), 60.9 (2), 46.5 (0), 44.6 (2), 29.2 (2), 27.7 (2), 21.8 (3), 21.0 (3), 20.3 (3), 14.2 (3).

LRMS *m/z* (CI, NH_3) 223 [$(M+H)^+$, 100%], 205 (25), 187 (45), 116 (20).

Microanalysis: Anal. Calcd for $C_{12}H_{21}ClO_4$: C, 54.44; H, 7.93. Found: C, 54.67; H, 7.96.

(*R*)-6-(3-Chloropropyl)-5,5-dimethyl-tetrahydro-2*H*-pyran-2,4-dione 4.12.



4.11
$C_{12}H_{21}ClO_4$
Mol. Wt.: 264.75

4.12
$C_{10}H_{15}ClO_3$
Mol. Wt.: 218.68

^{n}BuLi (2.3 M in hexanes, 100 mL, 230 mmol) was added to a stirred solution of diisopropylamine (34 mL, 240 mmol) in THF (330 mL) at 0°C over 15 min. After 20 min the mixture was cooled to –74°C and a solution of ester acetate **4.11** (29 g, 110 mmol) in THF (40+5 mL) was added dropwise over 15 min keeping the temperature of the reaction mixture below –68°C. The yellow solution was stirred at –74°C for 1.5 h and quenched with 2M $HCl_{(aq)}$ (280 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 120 mL). The combined organic extracts were washed with brine (100 mL), dried (Na_2SO_4) and concentrated. The residue was crystallised from CH_2Cl_2:hexanes to give β-ketolactone **4.12** (16.2 g, 74.0 mmol, 67%) as pale yellow heavy rock crystals. The mother liquor was concentrated and purified by column chromatography (SiO_2 35 g, hexanes:AcOEt 10-50%) to give a further portion of β-ketolactone **4.12** (2.1 g, 6.6 mmol, 9%). Double recrystallisation from CH_2Cl_2:hexanes afforded β-ketolactone **4.12** (14.7g, 67.1 mmol, 61%) as white heavy rock crystals: mp 103-105°C (CH_2Cl_2:hexanes). The enantiomeric excess was determined as >99% by chiral HPLC after a further two steps.

$[\alpha]_D^{20}$ +10.8 (*c* 1.0, $CHCl_3$).

ν_{max} film/cm^{-1} 1679 (s), 1605 (s), 1464 (s).

NMR assignments made using 2D H-H and C-H correlation spectra.

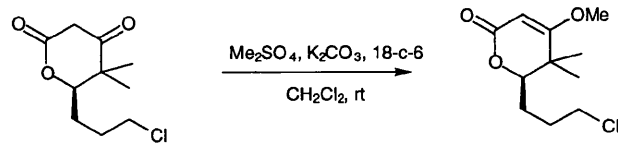
^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.35 (1H, dd, *J* = 10.8, 4.5 Hz, C15-H), 3.69 (1H, ddd, *J* = 11.1, 7.1, 4.8 Hz, C18-H_AH$_B$), 3.61 (1H, ddd, *J* = 11.1, 7.1, 5.1 Hz, C18-H$_A$$H_B$), 3.61 (1H, d, *J* = 19.0 Hz, C12-H$_A$$H_B$), 3.39 (1H, d, *J* = 18.9 Hz, C12-H_AH$_B$), 2.30-2.12 (1H, m), 2.04-1.64 (3H, m), 1.18 (3H, s, C14-Me), 1.10 (3H, s, C14-Me).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 205.4 (0), 167.3 (0), 82.5 (1), 46.9 (0), 45.0 (2), 44.5 (2), 28.8 (2), 26.1 (2), 20.5 (3), 17.6 (3).

LRMS *m/z* (CI, NH_3) 219 [(M+H)$^+$, 25%], 236 [(M+NH_4)$^+$, 30%], 112 (70), 70 (100).

Microanalysis: Anal. Calcd for $C_{10}H_{15}ClO_3$: C, 54.92; H, 6.86. Found: C, 54.93; H, 6.71.

(*R*)-6-(3-Chloropropyl)-4-methoxy-5,5-dimethyl-5,6-dihydro-2*H*-pyran-2-one 4.13.



4.12
$C_{10}H_{15}ClO_3$
Mol. Wt.: 218.68

4.13
$C_{11}H_{17}ClO_3$
Mol. Wt.: 232.70

A solution of β-ketolactone **4.12** (20.9 g, 95.5 mmol) and dimethyl sulphate (10.9 mL, 115.0 mmol) in CH_2Cl_2 (100 mL) was treated with K_2CO_3 (18.6 g, 134.5 mmol) and 18-crown-6 (250 mg, 1.0 mmol) at room temperature. The mixture was stirred vigorously for 15 h before being filtered through a pad of celite and concentrated *in vacuo*. The residue was purified by Kugelrohr distillation (200°C at 0.1 mm Hg) to give enol ether **4.13** (22.3 g, 95.5 mmol, 100%) as a colourless oil which formed a white solid on cooling: mp 56-57°C.

$[\alpha]_D^{22}$ –68.8 (*c* 1.7, $CHCl_3$).

ν_{max} film/cm^{-1} 1673 (s), 1603 (s).

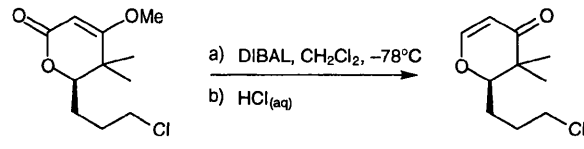
^1H NMR (300 MHz, $CDCl_3$): δ = 5.06 (1H, s, C12-H), 4.03 (1H, dd, *J* = 11.0, 2.2 Hz, C15-H), 3.72 (3H, s, OMe), 3.70-3.53 (2H, m, C18-H_2), 2.30-2.11 (1H, m), 1.97-1.62 (3H, m), 1.13 (3H, s, C14-Me), 1.10 (3H, s, C14-Me).

^{13}C NMR (90 MHz, $CDCl_3$): δ = 180.0 (0), 166.8 (0), 88.9 (1), 83.0 (1), 56.5 (3), 45.0 (2), 38.9 (0), 28.9 (2), 25.7 (2), 20.7 (3), 19.1 (3).

LRMS *m/z* (CI, NH_3) 233 [$(M+H)^+$, 100%], 126 (85), 112 (45), 70 (70).

Microanalysis: Anal. Calcd for $C_{11}H_{17}ClO_3$: C, 56.77; H, 7.31. Found: C, 56.74; H, 7.45.

(*R*)-6-(3-Chloropropyl)-5,5-dimethyl-5,6-dihydro-4*H*-pyran-4-one 2.2.



4.13
$C_{11}H_{17}ClO_3$
Mol. Wt.: 232.70

2.2
$C_{10}H_{15}ClO_2$
Mol. Wt.: 202.68

A solution of enol ether **4.13** (10.3 g, 44.2 mmol) in CH_2Cl_2 (80 mL) was cooled to –78°C to which DIBAL (neat, 8.7 mL, 48.6 mmol) was added in a dropwise fashion at a rate sufficient to keep the temperature below –70°C. When the addition was complete, the mixture was stirred for 40 min before the reaction was quenched by the careful addition of 2M $HCl_{(aq)}$ (250 mL). The mixture was stirred for a further 2 h at room temperature

then extracted with CH_2Cl_2 (3 x 50 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (50 mL), brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by Kugelrohr distillation (150°C at 0.1 mm Hg) to give dihydropyranone **2.2** (7.6 g, 37.4 mmol, 85%) as a pale yellow oil: $[\alpha]_D^{22}$ +135.1 (*c* 2.2, $CHCl_3$).

ν_{max} film/cm^{-1} 1674 (s), 1603 (s).

NMR assignments made using 2D H-H and C-H correlation spectra.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.29 (1H, d, *J* = 5.8 Hz, C11-H), 5.36 (1H, d, *J* = 5.8 Hz, C12-H), 4.02 (1H, dd, *J* = 10.2, 2.5 Hz, C15-H), 3.67-3.55 (2H, m, C18-H_2), 2.20-2.05 (1H, m, C17-H_AH_B), 1.96-1.75 (3H, m, C18-H_2 and C17-H_AH_B), 1.13 (3H, s, C14-Me), 1.04 (3H, s, C14-Me).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 198.4 (0), 161.4 (1), 105.2 (1), 85.7 (1), 44.6 (2), 44.3 (0), 28.9 (2), 25.4 (2), 19.6 (3), 17.8 (3).

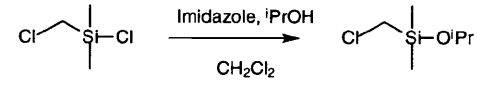
LRMS *m/z* (CI, NH_3) 203 [$(M+H)^+$, 100%], 167 (8), 112 (45), 132 (8), 98 (7), 69 (6), 41 (4).

HRMS (CI mode) [Found: $(M+H)^+$, 203.0840. $C_{10}H_{15}ClO_2$ requires *M*, 203.0839.

Microanalysis: Anal. Calcd for $C_{10}H_{15}ClO_2$: C, 59.26; H, 7.41. Found: C, 58.47; H, 7.24.

HPLC on Chiralcel OD 2 (4.6 x 250 mm), cyclohexane:isopropanol 98:2, major isomer 13.24 min, minor isomer 14.63 min established an ee of >99%.

Chloromethyldimethylisopropoxysilane.



$C_3H_8Cl_2Si$
Mol. Wt.: 143.09

$C_6H_{15}ClOSi$
Mol. Wt.: 166.72

Chloro-(chloromethyl)-dimethylsilane (50.0 mL, 54.3 g, 380.0 mmol) was added carefully to a solution of *iso*propanol (32.8 mL, 25.0 g, 415.0 mmol) and imidazole (28.3 g, 415.0 mmol) in CH_2Cl_2 (200 mL) at 0°C. The ice bath was removed and after stirring for 2 h the CH_2Cl_2 was removed *in vacuo*. The mixture was diluted with pentane (300 mL), filtered and concentrated *in vacuo*. The residue was vacuum distilled using short path apparatus (15 cm, ob 110°C, head 35°C at 50 mm Hg) to give a cloudy oil which was filtered through a cotton wool plug to give silane (50.2 g, 351.0 mmol, 92%) as a clear colourless oil.

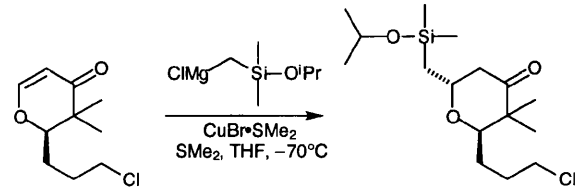
Literature bp 64-66°C at 54 mm Hg[118].

^{1}H NMR (270 MHz, $CDCl_3$): δ = 4.08 (1H, septet, J = 6.2 Hz, C*H*(CH_3)$_2$), 2.79 (2H, s, CH_2Cl), 1.18 (6H, d, J = 6.2 Hz, CH(C*H*$_3$)$_2$), 0.25 (6H, s, $SiMe_2$).

^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 78.7 (1), 42.9 (2), 38.7 (3, 2C), 9.9 (3, 2C).

(2*S*,6*R*)-6-(3-Chloropropyl)-2-[(isopropyloxydimethylsilyl)methyl]-5,5-dimethyl-tetrahydro-2*H*-pyran-4-one 5.2.

The 1,4-addition of an isopropoxymethyldimethylsilane Grignard to 2-cyclohexenone is described in the literature[90]. The author also reported that any attempt to add an isopropoxymethyldimethylsilane Grignard reagent to any other α,β-enones failed under a variety of conditions.



2.2
$C_{10}H_{15}ClO_2$
Mol. Wt.: 202.68

5.2
$C_{16}H_{31}ClO_3Si$
Mol. Wt.: 334.95

Magnesium turnings (5.60 g, 0.23 mol) were dried with a heat gun before a solution of THF (80 mL), 1,2-dibromoethane (250 μL) and chloromethylisopropoxydimethylsilane (2.0 mL, 11.1 mmol) were added. The mixture was heated gently until a strong exotherm indicated the reaction had begun. The remaining portion of chloromethylisopropoxydimethylsilane (18.6 mL, 103.2 mmol) was added carefully maintaining a temperature range of 50-60°C over a period of 20 min. After the addition was complete the mixture was left to cool to room temperature and stirred for 24 h.

To a mixture of CuBr•SMe_2 (694 mg) and SMe_2 (10.4 mL) at –78°C and was added the Grignard reagent over 30 min whilst maintaining a temperature below –60 °C. The mixture was diluted with THF (20 mL) and stirred at –70 °C for 10 min after which time enone **2.2** (9.0 g, 44.3 mmol) was added. After a further 1 h the mixture was left to warm to –30 °C and quenched by the addition of saturated aqueous NH_4Cl (200 mL), 10% aqueous ammonia solution (10 mL) and hexanes (200 mL). After stirring for 15 min the organic layer was removed and the aqueous layer extracted with hexanes (100 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to give the crude silane **5.2** (100%) which was used immediately in the next step. A sample was purified by column chromatography (SiO_2, hexanes:Et_2O 10-20% and Et_3N 1%) to give the following analytical data: $[\alpha]_D^{22}$ +8.7 (*c* 2.2, $CHCl_3$).

ν_{max} film/cm^{-1} 1712 (s).

^{1}H NMR (270 MHz, $CDCl_3$): δ = 4.19 (1H, dddd, J = 13.7 7.9, 6.2, 5.0 Hz, C11-H), 3.99 (1H, 7 lines, J = 6.2 Hz, C*H*Me_2), 3.67 (1H, dd, J = 10.6, 3.9 Hz, C15-H), 3.58 (2H, t, J = 6.2 Hz, C18-H_2), 2.55 (1H, 4 lines of ABX system, J = 14.3, 4.4 Hz, C12-H_AH_B), 2.48 (1H, 4 lines of ABX system, J = 14.3, 8.3 Hz, C12-H_AH_B), 2.10-1.50 (4H, m), 1.23 (3H, s, C14-Me), 1.14 [6H, d, 6.2 Hz, CH(C*H*$_3$)$_2$], 1.03 (3H, s, C14-Me), 1.05-0.98 (2H, m, C10-H_2), 0.16 (6H, s, $SiMe_2$).

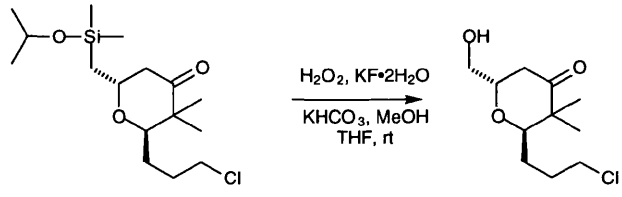
^{13}C NMR (75.0 MHz, $CDCl_3$): δ = 212.7 (0), 80.2 (1), 69.4 (1), 65.2 (1), 49.6 (0), 45.9 (2), 45.0 (2), 29.2 (2), 25.9 (3, 2C), 25.7 (2), 25.3 (2), 24.0 (3), 19.5 (3), -0.2 (3), -0.4 (3).

LRMS *m/z* (CI, NH_3) 335 [$(M+H)^+$, 15%], 275 (60), 229 (100), 170 (50).

Microanalysis: Anal. Calcd for $C_{16}H_{31}ClO_3Si$: C, 57.19; H, 9.16. Found: C, 57.40; H, 9.27.

(2*S*,6*R*)-6-(3-Chloropropyl)-2-hydroxymethyl-5,5-dimethyl-tetrahydro-2*H*-pyran-4-one 5.3.

Oxidation of a isopropoxydimethylsilyl group to a hydroxyl is described in the literature[91].



5.2
$C_{16}H_{31}ClO_3Si$
Mol. Wt.: 334.95

5.3
$C_{11}H_{19}ClO_3$
Mol. Wt.: 234.72

Crude silane **5.2** (43.3 mmol) was dissolved in an ice cold mixture of KF•2H_2O (6.28 g, 66.7 mmol), $KHCO_3$ (8.2 g, 82.0 mmol), THF (80 mL) and MeOH (80 mL). Aqueous hydrogen peroxide (30% wt. solution, 45.0 mL) was added in several portions. The mixture was stirred for 6 h at 0°C then saturated aqueous $Na_2S_2O_3$ (200 mL) was added carefully over 15 min whereupon the solution turned bright yellow (strong exotherm!). Water (200 mL) was added and the mixture extracted with CH_2Cl_2 (4 x 100 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2 60 g, hexanes:EtOAc 20-50%) to give the alcohol **5.3** (9.1 g, 38.7 mmol, 87% yield over 2 steps) as a clear colourless oil: $[\alpha]_D^{22}$ –8.7 (*c* 1.2, $CHCl_3$).

ν_{max} film/cm^{-1} 3436 (br), 1701 (s).

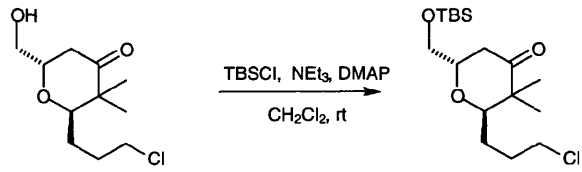
^{1}H NMR (270 MHz, $CDCl_3$): δ = 4.07-3.96 (1H, m, C11-H), 3.78 (1H, dd, J = 11.6, 3.7 Hz, C15-H), 3.71 (1H, 4 lines of ABX system, J = 11.8, 3.6 Hz, C10-H_AH_B), 3.62 (1H, 4 lines of ABX system, J = 11.8, 6.0 Hz, C10-H_AH_B), 3.57 (2H, t, J = 6.6 Hz, C18-H_2), 2.72 (1H, dd, J = 14.7, 10.0 Hz, C12-H_AH_B), 2.28 (1H, dd, J = 14.7, 4.2 Hz, C12-H_AH_B), 2.20-1.50 (5H, m), 1.28 (3H, s, C14-Me), 1.02 (3H, s, C14-Me).

^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 211.8 (0), 81.8 (1), 71.5 (1), 65.1 (2), 49.7 (0), 44.8 (2), 39.2 (2), 28.8 (2), 25.3 (2), 24.7 (3), 19.5 (3).

LRMS *m/z* (CI, NH_3) 235 [$(M+H)^+$, 30%], 252 [$(M+NH_4)^+$, 45%], 217 (10), 128 (100).

Microanalysis: Anal. Calcd for $C_{11}H_{19}ClO_3$: C, 56.29; H, 8.10. Found: C, 56.02; H, 7.98.

(2*S*,6*R*)-2-[(*tert*-Butyldimethylsilyloxy)methyl]-6-(3-chloropropyl)-5,5-dimethyl-tetrahydro-2*H*-pyran-4-one 5.4.



5.3
$C_{11}H_{19}ClO_3$
Mol. Wt.: 234.72

5.4
$C_{17}H_{33}ClO_3Si$
Mol. Wt.: 348.98

To a solution of the alcohol **5.3** (12.15 g, 51.7 mmol), triethylamine (93.0 mmol, 13.0 mL) and DMAP (230 mg) in CH_2Cl_2 (120 mL) was added *tert*-butyldimethylsilyl chloride (62.04 mmol, 9.35 g). The mixture was stirred at room temperature for 36 h whereupon saturated aqueous $NaHCO_3$ (200 mL), water (300 mL) and hexanes (200 mL) were added in succession. The organic layer was removed and the aqueous layer was extracted with hexanes (100 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was filtered through a pad of silica eluting with hexanes:EtOAc 5:1 to give the TBS ether **5.4** (17.0 g, 48.8 mmol, 94%) as a pale yellow oil: $[\alpha]_D^{22}$ +0.1 (*c* 2.4, $CHCl_3$).

ν_{max} film/cm^{-1} 1714 (s), 838 (s).

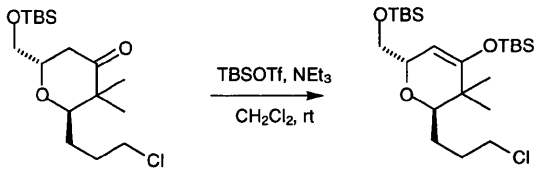
^1H NMR (270 MHz, $CDCl_3$): δ = 4.05-3.94 (1H, m, C11-H), 3.82 (1H, dd, *J* = 11.2, 3.3 Hz, C15-H), 3.72 (1H, 4 lines of ABX system, *J* = 10.8, 3.5 Hz, C10-H_AH_B), 3.69 (1H, 4 lines of ABX system, *J* = 10.8, 5.0 Hz, C10-H_AH_B), 3.59 (2H, t, *J* = 6.6 Hz, C18-H_2), 2.65 (1H, dd, *J* = 14.7, 8.7 Hz, C12-H_AH_B), 2.38 (1H, dd, *J* = 14.7, 5.0 Hz, C12-H_AH_B), 2.10-1.40 (4H, m), 1.23 (3H, s, C14-Me), 1.03 (3H, s, C14-Me), 0.90 (9H, s, ^{t}BuSi), 0.08 and 0.07 (3H each, s, Me_2Si).

^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 212.3 (0), 81.0 (1), 72.0 (1), 66.0 (2), 49.3 (0), 44.7 (2), 39.2 (2), 28.9 (2), 25.9 (3, 3C), 25.4 (2), 23.6 (3), 19.2 (3), 18.3 (0), –5.4 (3), –5.5 (3).

LRMS *m/z* (CI, NH_3) 366 [$(M+NH_4)^+$, 15%], 349 [$(M+H)^+$, 50%], 291 (35), 185 (100), 117 (80).

HRMS (CI mode) [Found: $(M+H)^+$, 349.1966. $C_{17}H_{34}ClO_3Si$ requires *M*, 349.1966.

(2*S*,6*R*)-4-(*tert*-Butyldimethylsilyloxy)-2-[(*tert*-butyldimethylsilyloxy)methyl]-6-(3-chloropropyl)-5,5-dimethyl-5,6-dihydro-2*H*-pyran 5.5.



5.4
$C_{17}H_{33}ClO_3Si$
Mol. Wt.: 348.98

5.5
$C_{23}H_{47}ClO_3Si_2$
Mol. Wt.: 463.24

To a solution of the ketone **5.4** (16.8 g, 48.2 mmol) and triethylamine (11.0 mL, 78.9 mmol) in CH_2Cl_2 (100 mL) was added dropwise *tert*-butyldimethylsilyl trifluoromethanesulfonate (13.3 mL, 57. 9 mmol) over 5 min. The yellow solution turned orange with a slight exotherm which was controlled by cooling with a water bath. After stirring at ambient temperature for 1.5 h the reaction was quenched by adding the reaction mixture to a mixture of saturated aqueous $NaHCO_3$ (200 mL) and hexanes (200 mL). The organic phase was removed, dried ($MgSO_4$) and concentrated *in vacuo* to give enol silane **5.5** as a pale yellow oil (100%) which was used immediately in the next step. A sample (200 mg) purified by column chromatography (SiO_2, hexanes:Et_2O 2%) gave: $[\alpha]_D^{22}$ –24.8 (*c* 2.0, $CHCl_3$).

ν_{max} film/cm^{-1} 1664 (s), 1471 (s), 1256 (s), 1126, 838 (s).

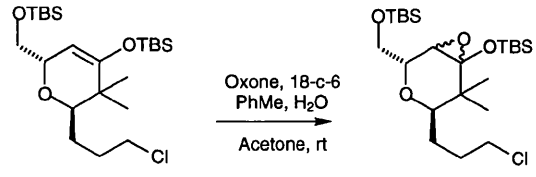
^1H NMR (270 MHz, $CDCl_3$): δ = 4.62 (1H, d, *J* = 3.3 Hz, C12-H), 4.22 (1H, ddd, *J* = 6.8, 5.2, 3.3, C11-H), 3.73-3.53 (3H, m), 3.52-3.42 (2H, m), 2.2-2.0 (1H, m), 1.9-1.4 (3H, m), 0.99 (3H, s, C14-Me), 0.97 (3H, s, C14-Me), 0.95 (9H, s, ^{t}BuSi), 0.90 (9H, s, ^{t}BuSi), 0.172 (3H, s, MeSi), 0.170 (3H, s, MeSi), 0.06 (6H, s, Me_2Si).

^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 156.7 (0), 99.0 (1), 77.6 (1), 72.9 (1), 65.2 (2), 45.4 (2), 38.9 (0), 30.2 (2), 26.5 (2), 26.1 (3, 3C), 25.9 (3, 3C), 22.3 (3), 19.6 (3), 18.4 (0, 2C), –4.2 (3), –4.7 (3), –5.2 (3, 2C).

LRMS *m/z* (CI, NH_3) 463 [$(M+H)^+$, 35%], 347 (45), 317 (100), 157 (70).

HRMS (CI mode) [Found: $(M+H)^+$, 463.2827. $C_{23}H_{48}ClO_3Si_2$ requires *M*, 463.2831.

(2*R*,3*S*,4*S*,6*R*)-4-(*tert*-Butyldimethylsilyloxy)-2-[(*tert*-butyldimethylsilyloxy)methyl]-6-(3-chloropropyl)-3,4-epoxy-5,5-dimethyl-tetrahydro-2*H*-pyran 5.6.



5.5
$C_{23}H_{47}ClO_3Si_2$
Mol. Wt.: 463.24

5.6
$C_{23}H_{47}ClO_4Si_2$
Mol. Wt.: 479.24

To a mechanically stirred solution of enol silane **5.5** (22.2 g, 48 mmol), $KHCO_3$ (121.0 g, 120.0 mmol), 18-crown-6 (1.11 g, 4.21 mmol), toluene (600 mL), acetone(120 mL) and water (1.20 L) was added oxone (200 g, 300 mmol) in portions over a period of 0.5 h. Beware gas evolution! After the addition was complete the mixture was stirred at room temperature for 30 min before the organic layer was removed. The aqueous phase was extracted with hexanes (2 x 100 mL) and the combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to give oxirane **5.6** (22.7 g, 47.3 mmol, 99%) as a pale yellow oil which was used immediately in the next step. A sample (200 mg) purified by column chromatography (SiO_2, with hexanes:Et_2O 1%) gave: $[\alpha]_D^{22}$ –8.6 (*c* 1.0, $CHCl_3$).

ν_{max} film/cm^{-1} 1664 (s), 1471 (s), 1256 (s), 1126, 838 (s).

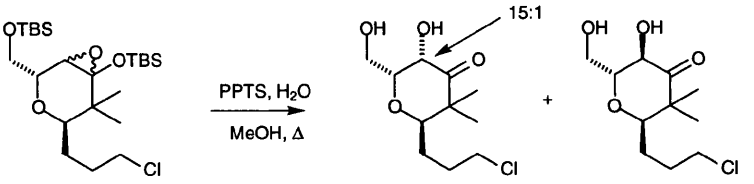
^{1}H NMR (270 MHz, $CDCl_3$): δ = 4.10 (1H, dt, *J* = 7.0, 3.3, C11-H), 3.69 (1H, dd, *J* = 9.7, 7.5 Hz, C10-H_AH_B), 3.61 (1H, dd, *J* = 9.7, 6.8 Hz, C10-H_AH_B), 3.60-3.45 (2H, m, C18-H_2), 3.41 (1H, d, *J* = 3.3 Hz, C12-H), 3.24 (1H, dd, *J* = 10.4, 1.0 Hz, C15-H), 2.1-1.9 (1H, m), 1.8-1.5 (2H, m), 1.4-1.2 (1H, m) 1.04 (3H, s, C14-Me), 0.96 (3H, s, C14-Me), 0.91 and 0.90 (9H each, s, ^{t}BuSi), 0.14, 0.09, 0.08 and 0.07 (3H each, s, Me_2Si).

^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 86.1 (0) 75.6 (1), 71.0 (1), 60.7 (1), 60.2 (2), 45.3 (2), 39.1 (0), 30.3 (2), 26.9 (2), 26.0 (3, 3C), 25.9 (3, 3C), 18.6 (3), 18.4 (0), 18.0 (0), 16.9 (3), –3.2 (3), –3.4 (3), –5.3 (3), –5.2 (3).

LRMS *m/z* (CI, NH_3) 479 [$(M+H)^+$, 65%], 443 [$(M+H–HCl)^+$, 20], 347 [$(M+H–TBSOH)^+$, 100].

HRMS (CI mode) [Found: $(M+NH_4)^+$, 496.3058. $C_{23}H_{51}ClO_4NSi_2$ requires *M*, 496.3045, [Found: $(M+H)^+$, 479.2748. $C_{23}H_{48}ClO_4Si_2$ requires *M*, 479.2780.

(2*R*,3*S*,6*R*)-6-(3-Chloropropyl)-3-hydroxy-2-hydroxymethyl-5,5-dimethyl-tetrahydro-2*H*-pyran-4-one 5.7a and (2*R*,3*R*,6*R*)-6-(3-Chloropropyl)-3-hydroxy-2-hydroxymethyl-5,5-dimethyl-tetrahydro-2*H*-pyran-4-one 5.7b.



5.6
$C_{23}H_{47}ClO_4Si_2$
Mol. Wt.: 479.24

5.7a
$C_{11}H_{19}ClO_4$
Mol. Wt.: 250.72

5.7b
$C_{11}H_{19}ClO_4$
Mol. Wt.: 250.72

A crude mixture of oxiranes **5.6** (1.19 g, 2.48 mmol), pyridinium *p*-toluenesulfonate (62 mg, 0.248 mmol), MeOH (5 mL) and water (0.25 mL) was heated at reflux for 18 h. After such time the reaction mixture was poured onto saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography (SiO_2 20 g, hexanes:AcOEt 20-70%) and ^1H NMR spectroscopic analysis (C_6D_6) of the mixture revealed doublets at δ = 4.29 (major) and 4.34 (minor) attributed to the methine proton adjacent to the carbonyl corresponding to a 15:1 mixture of diastereoisomeric diols **5.7a** and **5.7b** (537 mg, 2.14 mmol, 86%) as a colourless oil. The diastereoisomers were separated by recrystallisation (hexanes:Et_2O) to give pure desired diastereoisomer **5.7a** (335 mg, 1.34 mmol, 54%) as clear colourless crystals. The mother liquor was purified by column chromatography (SiO_2 15 g, hexanes:AcOEt 20-70%) to give another portion of the desired diastereoisomer **5.7a** (137 mg, 0.55 mmol, 22%) as a white solid and pure undesired diastereoisomer **5.7b** (30 mg, 0.12 mmol, 5%) as a white solid.

Desired diastereoisomer **5.7a**:

mp 60-60.5°C (hexanes:Et_2O)

$[\alpha]_D^{22}$= +90.0 (*c* 1.5, $CHCl_3$).

ν_{max} film/cm^{-1} 3417 (br), 1714 (s), 1463 (s), 1376 (m).

^1H NMR (270 MHz, $CDCl_3$): δ = 4.61 (1H, d, *J* = 7.9 Hz, C12-H), 4.43 (1H, ddd, *J* = 8.1, 5.2, 3.8, C11-H), 3.91 (1H, dd, *J* = 12.6, 5.2 Hz, C10-H_AH_B), 3.80 (1H, dd, *J* = 12.6, 3.5 Hz, C10-H_AH_B), 3.86-3.77 (2H, m), 3.70-3.58 (2H, m, C18-H_2), 2.20-1.75 (3H, m), 1.70-1.50 (2H, m), 1.18 (3H, s, C14-Me), 1.07 (3H, s, C14-Me).

^{13}C NMR (90 MHz, $CDCl_3$): δ = 213.3 (0), 79.0 (1) 78.1 (1), 70.7 (1), 62.4 (2), 49.0 (0), 45.1 (2), 30.0 (2), 27.0 (2), 20.3 (3), 19.4 (3).

LRMS *m/z* (CI, NH_3) 268 [$(M+NH_4)^+$, 65%], 251 [$(M+H)^+$, 50], 233 [$(M+H-H_2O)^+$, 25], 144 (100).

Microanalysis: Anal. Calcd for $C_{11}H_{19}ClO_4$: C, 52.69; H, 7.58. Found: C, 52.66; H, 7.45.

Undesired diastereoisomer **5.7b**:

mp 63-63.5°C (hexanes:Et_2O).

$[\alpha]_D^{22}$ +9.7 (*c* 1.8, $CHCl_3$).

ν_{max} film/cm^{-1} 3443 (br), 1714 (s), 1048 (s).

NMR assignments made using 2D C-H correlation spectra.

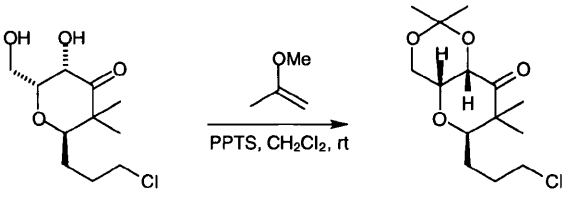
^1H NMR (270 MHz, $CDCl_3$): δ = 4.49 (1H, dm, *J* = 9.7 Hz, C15-H), 3.94 (1H, dd, *J* = 11.3, 3.0 Hz, C10-H_AH_B), 3.86 (1H, dd, *J* = 11.2, 4.6 Hz, C10-H_AH_B), 3.83 (1H, dd, *J* = 8.5 , 3.3 Hz, C12-H), 3.69 (1H, d, *J* = 3.2 Hz, C12-OH), 3.55 (2H, t, *J* = 6.2 Hz, C18-H_2), 3.46 (1H, ddd, *J* = 8.1, 4.6, 3.0 Hz, C11-H), 2.44 (1H, br s, CH_2-O*H*), 1.95-1.40 (4H, m), 1.41 (3H, s, C14-Me), 1.05 (3H, s, C14-Me).

^{13}C NMR (90 MHz, $CDCl_3$): δ = 212.7 (0), 83.6 (1) 76.8 (1), 70.0 (1), 63.2 (2), 49.7 (0), 44.6 (2), 28.1 (2), 26.0 (3), 24.5 (2), 19.5 (3).

LRMS *m/z* (CI, NH_3) 268 [$(M+NH_4)^+$, 100%].

Microanalysis: Anal. Calcd for $C_{11}H_{19}ClO_4$: C, 52.69; H, 7.58. Found: C, 52.61; H, 7.56.

(1*S*,6*R*,8*R*)-8-(3-Chloropropyl)-3,3,9,9-tetramethyl-2,4,7-trioxabicyclo[4,4,0]decan-10-one 5.8.



5.7a
$C_{11}H_{19}ClO_4$
Mol. Wt.: 250.72

5.8
$C_{14}H_{23}ClO_4$
Mol. Wt.: 290.78

A solution of diol **5.7a** (4.2 g, 16.6 mmol), 2-methoxypropene (3.2 mL, 33.0 mmol) and pyridinium *p*-toluenesulfonate (420 mg, 1.7 mmol) in CH_2Cl_2 (65 mL) was stirred at room temperature for 4.25 h. The reaction mixture was then poured onto saturated aqueous $NaHCO_3$ (300 mL) and extracted with CH_2Cl_2 (3 x 70 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2 120 g, hexanes:Et_2O 20-50%) to give the acetonide **5.8** (4.2 g, 14.3 mmol, 86%) as a colourless oil: $[\alpha]_D^{22}$ –1.5 (*c* 1.4, $CHCl_3$).

ν_{max} film/cm^{-1} 1726 (s), 1090 (S).

NMR assignments made using 2D C-H correlation spectra.

^{1}H NMR (360 MHz, $CDCl_3$): δ = 4.25 (1H, dd, J = 11.5, 2.5 Hz, C11-H), 4.21 (1H, d, J = 3.2 Hz, C12-H), 4.09 (1H, dd, J = 13.0, 3.6 Hz, C10-H_AH_B), 3.90 (1H, dd, J = 13.0, 2.8 Hz, C10-H_AH_B), 3.77 (1H, dd, J = 6.1, 3.2 Hz, C15-H), 3.62 (2H, t, J = 6.1 Hz, C18-H_2), 2.05-1.78 (2H, m), 1.70-1.60 (1H, m), 1.55-1.45 (1H, m) 1.45 (3H, s, CMe_2), 1.43 (3H, s, CMe_2), 1.33 (3H, s, C14-Me), 1.03 (3H, s, C14-Me).

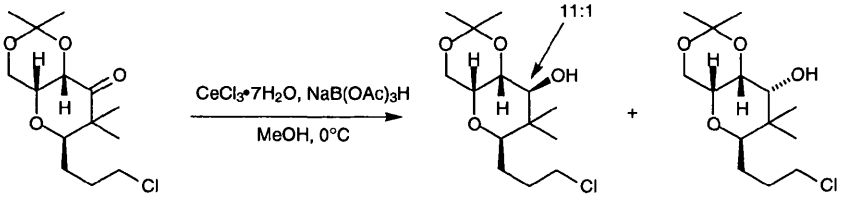
^{13}C NMR (90 MHz, $CDCl_3$): δ = 208.3 (0), 99.1 (0), 80.4 (1), 72.8 (1), 65.7 (1), 62.8 (2), 49.2 (0), 44.8 (2), 29.1 (2), 28.6 (3), 25.5 (2), 24.5 (3), 19.8 (3), 19.5 (3).

LRMS *m/z* (CI, NH_3) 291 [$(M+H)^+$, 100%], 275 (15), 203 (25), 132 (30), 101 (20), 73 (30).

Microanalysis: Anal. Calcd for $C_{14}H_{23}ClO_4$: C, 57.83; H, 7.91. Found: C, 57.79; H, 7.84.

(1*R*,6*R*,8*S*,10*S*)-8-(3-Chloropropyl)-3,3,9,9-tetramethyl-2,4,7-trioxabicyclo[4,4,0]decan-10-ol 5.9a and (1*R*,6*R*,8*S*,10*R*)-8-(3-Chloropropyl)-3,3,9,9-tetramethyl-2,4,7-trioxabicyclo[4,4,0]decan-10-ol 5.9b.

Reduction of a ketone to alcohol using $NaBH_4$ and $CeCl_3$•$7H_2O$ is described in the literature[38].



5.8
$C_{14}H_{23}ClO_4$
Mol. Wt.: 290.78

5.9a
$C_{14}H_{25}ClO_4$
Mol. Wt.: 292.80

5.9b
$C_{14}H_{25}ClO_4$
Mol. Wt.: 292.80

To a solution of ketone **5.8** (4.2 g, 14.3 mmol) in MeOH (218 mL) at 0°C was added $CeCl_3$•$7H_2O$ (6.4 g, 17.1 mmol). After stirring for 30 min, sodium triacetoxyborohydride (10.0 g, 47.5 mmol) was added. The reaction was stirred at 0°C for 4.25 h before saturated aqueous $NaHCO_3$ (500 mL) was carefully added and the MeOH was removed *in vacuo*. The resulting mixture was extracted with CH_2Cl_2 (3 x 100 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2 120 g, hexanes:Et_2O 50-70%) gave a mixture of diastereoisomeric alcohols **5.9a,b** (3.01 g, 10.3 mmol, 72%) as a white solid. ^{1}H NMR spectroscopic analysis of the mixture (C_6D_6) revealed singlets at δ = 0.78 (major) and 0.88 (minor) corresponding to **5.9a**:**5.9b** = 11:1. Crystallisation from hexanes:Et_2O gave diastereoisomerically pure alcohol **5.9a** (2.1 g, 7.3 mmol, 51%) as colourless needles. The mother liquor was purified by column chromatography (SiO_2 100 g, hexanes:Et_2O

20-70%) to give another portion of **5.9a** (310 mg, 1.06 mmol, 7%) and pure undesired diastereoisomer **5.9b** (206 mg, 0.70 mmol, 5%) as a white solid. Recrystallisation from hexanes:Et_2O gave white crystals for analysis.

Desired diastereoisomer **5.9a**:

mp 96-97°C (hexanes:Et_2O)

$[\alpha]_D^{22}$ +30.4 (*c* 1.2, $CHCl_3$).

ν_{max} film/cm^{-1} 3437 (br), 1462 (s), 1377 (s).

^1H NMR (270 MHz, C_6D_6): δ = 3.77 (1H, dd, *J* = 12.4, 3.3 Hz, C10-H_AH_B), 3.67 (1H, dd, *J* = 12.4, 3.7 Hz, C10-H_AH_B), 3.60 (1H, dd, *J* = 3.7, 3.1 Hz, C12-H), 3.44 (1H, q, *J* = 3.5 Hz, C11-H), 3.35 (1H, d, *J* = 3.9 Hz, OH), 3.34 (1H, dd, *J* = 3.8, 2.9 Hz, C13-H), 3.25 (3H, t, *J* = 6.8 Hz, C18-H_2, C15-H), 2.10-1.90 (1H, m), 1.85-1.80 (1H, m), 1.60-1.40 (1H, m), 1.45 (3H, s, CMe_2), 1.40-1.25 (1H, m), 1.24 and 1.23 (3H each, s, CMe_2 and C14-Me), 0.80 (3H, s, C14-Me).

^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 98.5 (0), 80.3 (1), 75.0 (1), 70.5 (1), 62.9 (2), 60.3 (1), 45.2 (2), 36.4 (0), 29.8 (2), 28.9 (3), 27.1 (3), 24.6 (2), 21.2 (3), 19.8 (3).

LRMS *m/z* (CI, NH_3) 293 [$(M+H)^+$, 100%], 277 (20), 217 (20).

Microanalysis: Anal. Calcd for $C_{14}H_{25}ClO_4$: C, 57.43; H, 8.55. Found: C, 57.42; H, 8.55.

Undesired diastereoisomer **5.9b**:

mp 89-90°C (hexanes:Et_2O).

$[\alpha]_D^{22}$ +47.0 (*c* 1.0, $CHCl_3$).

ν_{max} film/cm^{-1} 3516 (m), 1461 (s), 1377 (S).

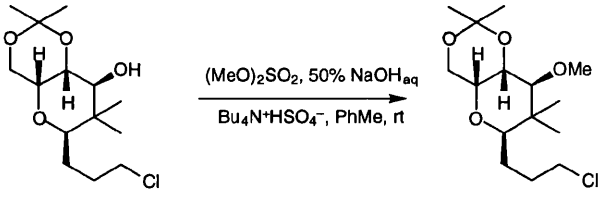
^1H NMR (270 MHz, C_6D_6): δ = 3.66 (1H, dd, *J* = 12.7, 1.9 Hz, C10-H_AH_B), 3.59 (1H, dd, *J* = 4.2, 2.1 Hz, C12-H), 3.53 (1H, dd, *J* = 12.6, 2.9 Hz, C10-H_AH_B), 3.39 (1H, dd, *J* = 11.5, 3.1 Hz, C15-H), 3.37-3.30 (1H, m, C13-H), 3.28-3.10 (2H, m, C18-H_2), 2.72 (1H, q, *J* = 2.1 Hz, C11-H), 2.31 (1H, d, *J* = 10.6 Hz, OH), 1.65-1.15 (4H, m), 1.37 and 1.27 (3H each, s, CMe_2), 1.13 (3H, s, C14-Me), 0.88 (3H, s, C14-Me).

^{13}C NMR (90 MHz, $CHCl_3$): δ = 98.9 (0), 81.8 (1), 71.6 (1), 67.5 (1), 63.2 (2), 62.7 (1), 45.1 (2), 37.7 (0), 29.4 (3), 29.1 (2), 24.6 (3), 22.6 (3), 22.6 (2), 18.7 (3).

LRMS *m/z* (CI, NH_3) 310 [$(M+NH_4)^+$, 60%], 293 [$(M+H)^+$, 55].

Microanalysis: Anal. Calcd for $C_{14}H_{25}ClO_4$: C, 57.43; H, 8.55. Found: C, 57.36; H, 8.47.

(1*R*,6*R*,8*R*,10*S*)-8-(3-Chloropropyl)-10-methoxy-3,3,9,9-tetramethyl-2,4,7-trioxabicyclo[4,4,0]decan 5.11.



5.9a
$C_{14}H_{25}ClO_4$
Mol. Wt.: 292.80

5.11
$C_{15}H_{27}ClO_4$
Mol. Wt.: 306.83

Dimethyl sulfate (3.0 mL, 4.0 g, 32.0 mmol) was added to a vigorously stirred mixture of alcohol **5.9a** (2.42 g, 8.27 mmol), tetrabutylammonium hydrogen sulphate (573 mg, 1.70 mmol), toluene (32 mL) and 50% aqueous solution of NaOH (21 mL). The reaction mixture was stirred vigorously for 14 h whereupon MeOH (9 mL) was added and after a further 15 min the mixture was treated with H_2O (220 mL). The mixture was extracted with CH_2Cl_2 (3 x 80 mL), and the combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2 80 g, hexanes:Et_2O 10-25%) to give methyl ether **5.11** (2.47 g, 8.06 mmol, 97%) as a colourless oil which solidified on standing: mp 49-50 °C (MeOH:H_2O)

$[\alpha]_D^{22}$ –1.9 (*c* 1.2, $CHCl_3$).

ν_{max} film/cm^{-1} 1454 (s), 1381 (s), 1276 (s), 1094 (s).

^1H NMR (270 MHz, $CDCl_3$): δ = 4.08 (1H, dd, *J* = 12.7, 2.5 Hz, C10-H_AH_B), 3.90 (1H, t, *J* = 2.3 Hz, C12-H), 3.86 (1H, dd, *J* = 12.7, 1.7 Hz, C10-H_AH_B), 3.59 (2H, t, *J* = 6.6 Hz, C18-H_2), 3.55-3.45 (2H, m, C11-H and C15-H), 3.39 (3H, s, OMe), 2.84 (1H, d, *J* = 2.7 Hz, C13-H), 2.20-2.05 (1H, m), 1.95-1.45 (3H, m), 1.47 and 1.45 (3H each, s, CMe_2), 1.25 (3H, s, C14-Me), 0.93 (3H, s, C14-Me).

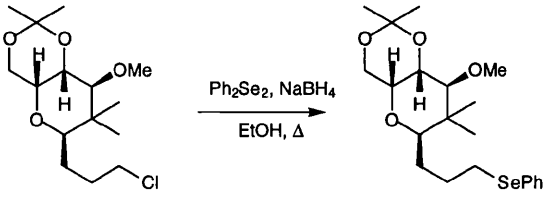
^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 98.6 (0), 85.8 (1), 80.5 (1), 67.3 (1), 63.6 (2), 60.7 (1), 59.3 (3), 45.6 (2), 36.9 (0), 30.5 (2), 29.6 (3), 28.3 (3), 25.1 (2), 22.3 (3), 19.6 (3).

LRMS *m/z* (CI, NH_3) 307 [$(M+H)^+$, 100%].

Microanalysis: Anal. Calcd for $C_{15}H_{27}ClO_4$: C, 58.73; H, 8.81. Found: C, 57.80; H, 8.74.

(1*R*,6*R*,8*R*,10*S*)-10-Methoxy-3,3,9,9-tetramethyl-8-(3-phenylselenylpropyl)-2,4,7-trioxabicyclo[4,4,0]decan 5.12.

Substitution of a halide with sodium phenylselenide is described in the literature[119].



5.11
$C_{15}H_{27}ClO_4$
Mol. Wt.: 306.83

5.12
$C_{21}H_{32}O_4Se$
Mol. Wt.: 427.44

Sodium borohydride (208 mg, 5.50 mmol) was added in batches into a stirred yellow suspension of diphenyl diselenide (773 mg, 2.47 mmol) in anhydrous EtOH (11.5 mL) to cause exothermic reaction and gas evolution. A solution of chloride **5.11** (990 mg, 3.23 mmol) in anhydrous EtOH (3 x 2.5 mL) was transferred *via* cannula to the solution of sodium phenyl selenide and the resulting mixture was heated at reflux for 40 min. After cooling to room temperature the reaction mixture was diluted with Et_2O (160 mL) and extracted with 2 M $NaOH_{(aq)}$ (2 x 35 mL) and brine. The organic layer was dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography (SiO_2 10 g, hexanes:Et_2O 0-30%) to give selenide **5.12** (1.40 g, 100%) as a colourless oil: $[\alpha]_D^{22}$ +17.9 (*c* 1.4, $CHCl_3$).

ν_{max} film/cm^{-1} 1579 (s).

^{1}H NMR (270 MHz, $CDCl_3$): δ = 7.52-7.45 (2H, m), 7.29-7.21 (3H, m),.4.01 (1H, dd, J = 12.7, 2.5 Hz, C10-H_AH_B), 3.87 (1H, t, J = 2.3 Hz, C12-H), 3.76 (1H, dd, J = 12.7, 1.7 Hz, C10-H_AH_B), 3.46 (1H, dd, J = 12.2, 2.9 Hz, C15-H), 3.42 (1H, q, J = 2.3 Hz, C11-H), 3.38 (3H, s, OMe), 3.01 (1H, ddd, J = 11.8, 7.9, 6.0 Hz, C18-H_AH_B), 2.88 (1H, ddd, J = 12.0, 7.9, 7.1 Hz, C18-H_AH_B), 2.81 (1H, d, J = 2.7 Hz, C13-H), 2.11 (1H, dddd, J = 14.1, 12.2, 9.1, 4.6 Hz, C16-H), 1.90-1.60 (3H, m), 1.46 and 1.44 (3H each, s, CMe_2), 1.22 (3H, s, C14-Me), 0.88 (3H, s, C14-Me).

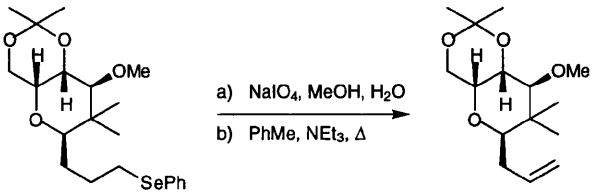
^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 132.7 (1, 2C), 130.5 (0), 129 (1, 2C), 126.7 (1), 98.3 (0), 84.9 (1), 80.6 (1), 66.5 (1), 63.4 (2), 59.4 (3), 59.3 (1), 36.3 (0), 29.4 (3), 27.9 (3), 27.8 (2), 27.0 (2), 26.9 (2), 22.4 (3), 18.8 (3).

LRMS *m/z* (CI, NH_3) 446 [$(M+NH_4)^+$, 17%], 429 [$(M+H)^+$, 9].

Microanalysis: Anal. Calcd for $C_{21}H_{32}O_4Se$: C, 59.02; H, 7.49. Found: C, 59.27; H, 7.61.

(1*R*,6*R*,8*R*,10*S*)-10-Methoxy-3,3,9,9-tetramethyl-8-(prop-2-enyl)-2,4,7-trioxabicyclo[4,4,0]decan 5.13.

Oxidation of a selenide to a selenoxide and elimination of a selenoxide are described in the literature[13, 14].



5.12
$C_{21}H_{32}O_4Se$
Mol. Wt.: 427.44

5.13
$C_{15}H_{26}O_4$
Mol. Wt.: 270.36

Sodium metaperiodate (1.01 g, 4.70 mmol) was added in several portions to a stirred mixture of selenide **5.12** (1.31 mg, 3.23 mmol), water (18 mL) and MeOH (45 mL) at room temperature. The reaction mixture was stirred for 15 min and then diluted with water (55 mL) and extracted with CH_2Cl_2 (3 x 40 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. The residue was treated with toluene (4.5 mL) and triethylamine (4.5 mL) and heated at reflux for 10 min. The yellow reaction mixture was cooled to room temperature, poured onto saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (3 x 40 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography (SiO_2 30 g, hexanes:ether 0-20%) to give alkene **5.13** (780 mg, 3.20 mmol, 99%) as a colourless oil which solidified on storage in the refrigerator: mp 33-33.5 °C (MeOH:H_2O).

$[\alpha]_D^{22}$ –11.2 (*c* 1.1, $CHCl_3$).

ν_{max} film/cm^{-1} 1651 (m) 1463 (m), 1390 (s).

NMR assignments made using 2D C-H correlation spectra.

^{1}H NMR (270 MHz, $CDCl_3$): δ = 5.82 (1H, dddd, *J* = 17.6, 10.2, 7.5, 6.0 Hz, C17-H), 5.03 (1H, dq, *J* = 16.9, 1.7 Hz, C18-H_{trans}), 4.98 (1H, dm, *J* = 10.2 Hz, C18-H_{cis}), 4.05 (1H, dd, *J* = 12.7, 2.7 Hz, C10-H_AH_B), 3.90 (1H, t, *J* = 2.5 Hz, C12-H), 3.82 (1H, dd, *J* = 12.7, 2.1 Hz, C10-H_AH_B), 3.59 (1H, dd, *J* = 12.0, 3.7 Hz, C15-H), 3.53 (1H, q, *J* = 2.3 Hz, C11-H), 3.40 (3H, s, OMe), 2.84 (1H, d, *J* = 2.7 Hz, C13-H), 2.79 (1H, dddt, *J* = 15.0, 11.4, 7.3, 1.1 Hz, C16-H_AH_B), 2.17 (1H, dddt, *J* = 15.5, 5.4, 3.5, 1.5 Hz, C16-H_AH_B), 1.47 and 1.44 (3H each, s, CMe_2), 1.25 (3H, s, C14-Me), 0.93 (3H, s, C14-Me).

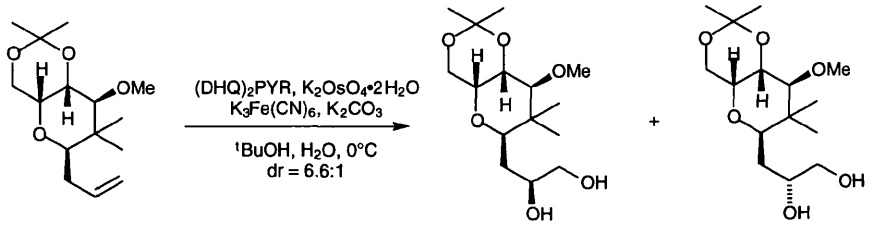
^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 136.7 (1), 115.2 (2), 98.1 (0), 84.8 (1), 80.7 (1), 66.3 (1), 63.2 (2), 59.3 (3), 59.1 (1), 36.2 (0), 32.2 (2), 29.2 (3), 27.6 (3), 22.4 (3), 18.7 (3).

LRMS *m/z* (CI, NH_3) 271 [$(M+H)^+$, 30%], 229 (80), 171 (70), 101 (55), 85 (80), 71 (100).

Microanalysis: Anal. Calcd for $C_{15}H_{26}O_4$: C, 66.66; H, 9.62. Found: C, 66.64; H, 9.61.

(1*R*,6*R*,8*R*,10*S*)-8-[(2*S*)-2,3-Dihydroxypropyl]-10-methoxy-3,3,9,9-tetramethyl-2,4,7-trioxabicyclo[4,4,0]decan 5.14a and (1*R*,6*R*,8*R*,10*S*)-8-[(2*R*)-2,3-dihydroxypropyl]-10-methoxy-3,3,9,9-tetramethyl-2,4,7-trioxabicyclo[4,4,0]decan 5.14b.

The asymmetric dihyroxylation was performed according to literature procedure.[120]



5.13
$C_{15}H_{26}O_4$
Mol. Wt.: 270.36

5.14a
$C_{15}H_{28}O_6$
Mol. Wt.: 304.38

5.14b
$C_{15}H_{28}O_6$
Mol. Wt.: 304.38

Alkene **5.13** (918 mg, 3.4 mmol) and $(DHQ)_2PYR$ (34 mg, 0.039 mmol) were stirred in warm ^tBuOH (21 mL) until the ligand dissolved (*ca* 30 min). After cooling to room temperature water (21 mL), $K_3Fe(CN)_6$ (3.4 g, 10.32 mmol) and K_2CO_3 (1.43 g, 10.36 mmol) were added and the mixture was cooled to 0°C. Potassium osmate dihydrate (12.5 mg, 0.034 mmol) was then added. The reaction mixture was stirred for 3 h at 0°C, treated with saturated aqueous Na_2SO_3 (42 mL) and stirred for 15 min then extracted with CH_2Cl_2 (3 x 100 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated to give a 6.6:1 mixture of diols **5.14a,b** according to integration of the singlets at $\delta = 0.86$ (major) and 0.92 (minor) revealed in the ^1H NMR spectrum (C_6D_6) of the mixture. The diastereoisomers were separated by column chromatography (SiO_2 20 g, CH_2Cl_2:methanol 0-4%) to afford pure major diol **5.14a** (860 mg, 83%) and a mixture of diols **5.14a,b** (165 mg, 16%). The desired isomer **5.14a** was recrystallised from hexanes:Et_2O to form thick colourless needles: mp 102-103°C (Et_2O:hexanes).

$[\alpha]_D^{17}$ –19.1 (*c* 1.0, $CHCl_3$).

ν_{max} CCl_4/cm^{-1} 3441 (br).

NMR assignments made using 2D H-H and C-H correlation spectra.

^1H NMR (270 MHz, $CDCl_3$): $\delta = 4.09$ (1H, dd, J = 12.9, 2.5 Hz, C10-H_AH_B), 3.93 (1H, t, J = 2.5 Hz, C12-H), 3.95-3.85 (1H, m, C17-H), 3.86-3.73 (3H, m), 3.64 [1H, m (in presence of D_2O appears as dd, J = 11.2, 3.7 Hz), C18-H_AH_B], 3.50 [1H, m (in presence of D_2O appears as dd, J = 11.2, 6.0 Hz), C18-H_AH_B], 3.40 (3H, s, OMe), 2.86 (1H, d, J = 2.9 Hz, C13-H), 2.20 (1H, br, OH), 2.19 (1H, ddd, J = 15.1, 12.0, 8.9 Hz, C16-H_AH_B), 1.67 (1H, br, OH), 1.56 (1H, ddd, J = 3.5, 2.1 Hz, signal collapses with *gem*-Me groups, C16-H_AH_B), 1.47 and 1.45 (3H each, s, CMe_2), 1.23 (3H, s, C14-Me), 0.93 (3H, s, C14-Me).

^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 98.4 (0), 84.5 (1), 81.1 (1), 72.5 (1), 66.5 (1), 66.0 (2), 63.2 (2), 60.3 (1), 59.3 (3), 36.5 (0), 30.0 (2), 29.2 (3), 27.4 (3), 21.9 (3), 18.8 (3).

LRMS *m/z* (CI, NH_3) 305 [$(M+H)^+$, 50%], 289 (25), 273 (15), 247 (55), 87 (100).

Microanalysis: Anal. Calcd for $C_{15}H_{28}O_6$: C, 59.21; H, 9.21. Found: C, 59.31; H, 9.11.

A sample of undesired diastereoisomer **5.14b** obtained by further column chromatography of a mixture of **5.14a,b** gave: mp 104-104.5°C (Et_2O:hexanes).

$[\alpha]_D^{17}$ +6.9 (*c* 0.9, $CHCl_3$).

ν_{max} CCl_4/cm^{-1} 3441 (br).

NMR assignments made using 2D H-H and C-H correlation spectra.

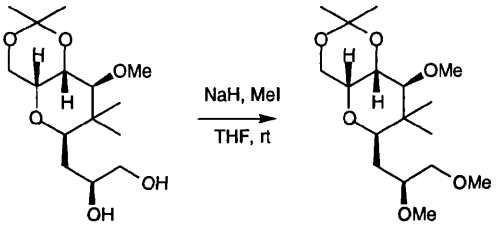
^1H NMR (400 MHz, $CDCl_3$): δ = 4.08 (1H, dd, *J* = 12.8, 2.0 Hz, C10-H_AH_B), 3.91 (1H, t, *J* = 2.0 Hz, C12-H), 3.90-3.80 (3H, m), 3.57 [1H, m (in presence of D_2O appears as dd, *J* = 11.2, 3.2 Hz), C18-H_AH_B], 3.52 (1H, m), 3.50 [1H, m (in presence of D_2O appears as dd, *J* = 11.2, 7.6 Hz, C18-H_AH_B], 3.39 (3H, s, OMe), 2.92 (1H, d, *J* = 4.8 Hz, C17-OH), 2.85 (1H, d, *J* = 2.4 Hz, C13-H), 2.39 (1H, dd, *J* = 8.0, 4.0 Hz, C18-OH), 2.29 (1H, dd, *J* = 8.1, 4.1 Hz, OH), 2.12 (1H, ddd, *J* = 14.8, 12.4, 2.8 Hz, C16-H_AH_B), 1.50 (3H, s, OC(Me)O), 1.46 (3H, s, OC(Me)O), 1.43 (1H, ddd, *J* = 14.8, 10.0, 3.2 Hz, C16-H_AH_B), 1.26 (3H, s, C14-Me), 0.92 (3H, s, C14-Me).

^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 98.5 (0), 84.5 (1), 77.7 (1), 68.9 (1), 67.7 (2), 66.4 (1), 63.3 (2), 59.5 (1, 2, 2C), 36.0 (0), 30.3 (2), 29.3 (3), 27.8 (3), 22.5 (3), 18.6 (3).

LRMS *m/z* (CI, NH_3) 305 [$(M+H)^+$, 5%], 289 (20), 273 (10), 231 (15), 87 (100).

Microanalysis: Anal. Calcd for $C_{15}H_{28}O_6$: C, 59.21; H, 9.21. Found: C, 59.23; H, 9.29.

(1*R*,6*R*,8*R*,10*S*)-10-Methoxy-8-[(2*S*)-2,3-dimethoxypropyl]-3,3,9,9-tetramethyl-2,4,7-trioxabicyclo[4,4,0]decan 5.15.



5.14a
$C_{15}H_{28}O_6$
Mol. Wt.: 304.38

5.15
$C_{17}H_{32}O_6$
Mol. Wt.: 332.43

Sodium hydride (500 mg, 60% in oil, 12.5 mmol) was added to a stirred solution of diol **5.14a** (1.65 g, 4.96 mmol) and methyl iodide (1.0 mL, 16.7 mmol) in THF (18 mL) at 0°C. After 5 min the cooling bath was removed and the reaction mixture was stirred at room temperature for 7 h and then poured onto brine and extracted with CH_2Cl_2 (3 x 40 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography (SiO_2 20 g, hexanes:AcOEt 10-50%) to give methyl ether **5.15** (1.55 g, 4.68 mmol, 94%) as a colourless oil: $[\alpha]_D^{23}$ +7.6 (*c* 1.1, $CHCl_3$).

ν_{max} film/cm^{-1} 2878 (s), 2821 (s), 1455 (s), 1380 (s), 1094 (s), 850 (s).

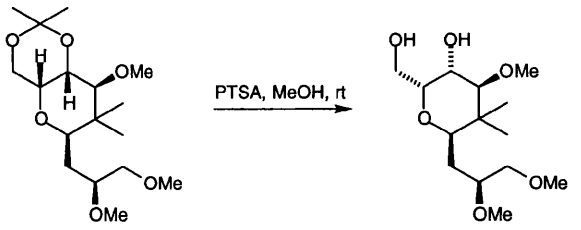
^{1}H NMR (270 MHz, $CDCl_3$): δ = 4.09 (1H, dd, *J* = 12.6, 2.5 Hz, C10-H$_A$*H*$_B$), 3.93 (1H, t, *J* = 2.1 Hz, C12-H), 3.85 (1H, dd, *J* = 12.7, 1.7 Hz, C10-*H*$_A$H$_B$), 3.63 (1H, q, *J* = 1.9 Hz, C11-H), 3.57 (1H, dd, *J* = 12.3, 3.0 Hz, C15-H), 3.51 (1H, 4 lines of ABX system, *J* = 10.2, 3.5 Hz, C18-H$_A$*H*$_B$), 3.46 (1H, 4 lines of ABX system, *J* = 10.2, 5.0 Hz, C12-*H*$_A$H$_B$), 3.42-3.32 (1H, m, C17-H), 3.37 (6H, s, OMe), 3.36 (3H, s, OMe), 2.83 (1H, d, *J* = 2.5 Hz, C13-H), 2.35 (1H, ddd, *J* = 14.8, 12.4, 4.6 Hz, C16-H$_A$*H*$_B$), 1.57 (1H, ddd, *J* = 14.9, 7.9, 3.1 Hz, C16-*H*$_A$H$_B$), 1.47 and 1.44 (3H each, s, CMe_2), 1.23 (3H, s, C14-Me), 0.91 (3H, s, C14-Me).

^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 98.3 (0), 84.8 (1), 78.7 (1), 78.6 (1), 73.2 (2), 66.5 (1), 63.5 (2), 59.7 (1), 59.4 (3), 59.2 (3), 57.2 (3), 36.3 (0), 29.4 (3), 28.2 (2), 27.7 (3), 22.3 (3), 18.7 (3).

LRMS *m/z* (CI, NH_3) 350 [$(M+NH_4)^+$, 55%], 333 [$(M+H)^+$, 100].

HRMS (CI mode) Found: $(M+H)^+$, 333.2270. $C_{17}H_{33}O_6$ requires *M*, 333.2277.

(2*R*,3*R*,4*S*,6*R*)-2-Hydroxymethyl-4-methoxy-6-[(*S*)-2,3-dimethoxypropyl]-5,5-dimethyl-tetrahydro-2*H*-pyran-3-ol 2.1.

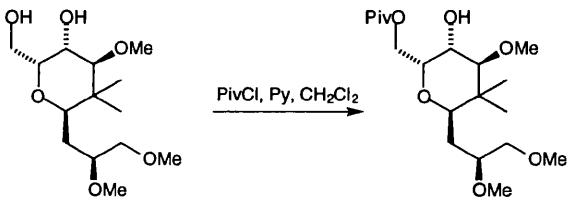


5.15
$C_{17}H_{32}O_6$
Mol. Wt.: 332.43

2.1
$C_{14}H_{28}O_6$
Mol. Wt.: 292.37

A solution of acetal **5.15** (1.38g, 4.15 mmol) and *p*-toluenesulfonic acid (16 mg, 0.083 mmol) in MeOH (14 mL) was stirred at room temperature for 45 min. $NaHCO_3$ (0.4 g, 9.76 mmol) was then added and the mixture concentrated. The residue was taken up in CH_2Cl_2, filtered through a pad of celite and concentrated to give crude diol **2.1** (100%) whose ^1H and ^{13}C NMR spectroscopic data were in agreement with that reported in the literature[17]. The mixture was used in the next step without further purification.

(2*R*,3*R*,4*S*,6*R*)-2-[(*tert*-Butylcarbonyloxy)methyl]-4-methoxy-6-[(2*S*)-2,3-dimethoxypropyl]-5,5-dimethyl-tetrahydro-2*H*-pyran-3-ol 5.17.

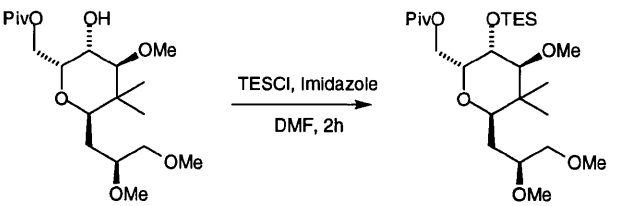


2.1
$C_{14}H_{28}O_6$
Mol. Wt.: 292.37

5.17
$C_{19}H_{36}O_7$
Mol. Wt.: 376.48

As previously described on a 4.21 mmol scale with a quantitative yield over two steps[17].

(2*R*,3*R*,4*S*,6*R*)-2-[(*tert*-Butylcarbonyloxy)methyl]-4-methoxy-6-[(2*S*)-2,3-dimethoxypropyl]-5,5-dimethyl-3-(triethylsilyloxy)-tetrahydro-2*H*-pyran 5.18.



5.17
$C_{19}H_{36}O_7$
Mol. Wt.: 376.48

5.18
$C_{25}H_{50}O_7Si$
Mol. Wt.: 490.75

A solution of alcohol **5.17** (1.58 g, 4.21 mmol), imidazole (331 mg, 5.0 mmol) and chlorotriethylsilane (0.81 mL, 4.72 mmol) in anhydrous DMF (6 mL) was stirred at room temperature for 2 h. The reaction mixture was then poured onto water (60 mL) and extracted with hexanes (3 x 40 mL). The combined organic extracts were

dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography (SiO_2 15 g, hexanes:AcOEt 0-10%) to give silyl ether **5.18** (1.96 g, 4.17 mmol, 99%) as colourless rock crystals: mp 41-42°C (MeOH:H_2O).

$[\alpha]_D^{23}$ +70.9 (*c* 1.2, $CHCl_3$).

ν_{max} CCl_4/cm^{-1} 1730 (s).

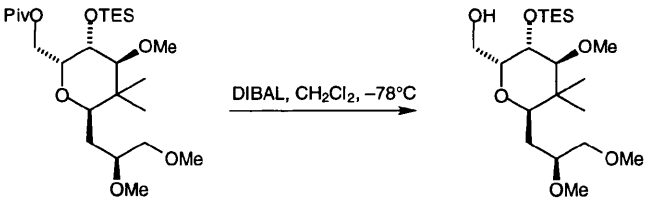
^1H NMR (270 MHz, $CDCl_3$): δ = 4.52 (1H, dd, *J* = 12.4, 9.5 Hz, C10-H_AH_B), 4.27 (1H, dd, *J* = 12.4, 2.3 Hz, C10-H_AH_B), 4.12 (1H, ddd, *J* = 9.5, 6.9, 4.3 Hz, C11-H), 3.93 (1H, dd, *J* = 9.5, 6.8 Hz, C12-H), 3.50 (3H, s, OMe), 3.50-3.30 (4H, m), 3.361 (3H, s, OMe), 3.359 (3H, s, OMe), 2.78 (1H, d, *J* = 9.6 Hz, C13-H), 1.72-1.63 (2H, m, C16-H_2), 1.23 (9H, s, ^{t}Bu), 0.973 (3H, t, *J* = 8.1 Hz, CH_3CH_2), 0.971 (6H, t, *J* = 8.1 Hz, CH_3CH_2), 0.94 (3H, s, C14-Me), 0.87 (3H, s, C14-Me), 0.633 (4H, q, *J* = 7.9 Hz, CH_3CH_2), 0.629 (2H, q, *J* = 7.9 Hz, CH_3CH_2).

^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 178.6 (0), 86.5 (1), 77.9 (1), 75.3 (1), 73.8 (1), 73.4 (2), 70.2 (1), 62.3 (3), 60.1 (2), 59.3 (3), 56.9 (3), 41.1 (0), 38.8 (0), 29.8 (2), 27.3 (3, 3C), 23.4 (3), 14.0 (3), 6.8 (3, 2C), 6.7 (3), 5.9 (2), 4.9 (2, 2C).

LRMS *m/z* (CI, NH_3) 508 [$(M+NH_4)^+$, 30%], 491 [$(M+H)^+$, 20].

Microanalysis: Anal. Calcd for $C_{25}H_{50}O_7Si$: C, 61.22; H, 10.20. Found: C, 61.08; H, 10.10.

(2*R*,3*R*,4*S*,6*R*)-2-Hydroxymethyl-4-methoxy-6-[(2*S*)-2,3-dimethoxypropyl]-5,5-dimethyl-3-[(triethylsilyl)oxy]-tetrahydro-2*H*-pyran 5.19.



5.18
$C_{25}H_{50}O_7Si$
Mol. Wt.: 490.75

5.19
$C_{20}H_{42}O_6Si$
Mol. Wt.: 406.63

DIBAL (neat, 2 mL, 11.2 mmol) was added dropwise to a stirred solution of ester **5.18** (3.03 g, 6.17 mmol) in CH_2Cl_2 (25 mL) at –78 °C. The reaction mixture was stirred for 30 min before being treated with saturated aqueous Na_2SO_4 (2 mL) and CH_2Cl_2 (50 mL). After stirring for a further 1 h at room temperature the resulting milky suspension was filtered through a pad of celite and concentrated to give alcohol **5.19** (2.47 g, 98%) as a colourless oil: $[\alpha]_D^{20}$ +57.8° (*c* 1.0, $CHCl_3$).

ν_{max} film/cm^{-1} 3476 (br).

^{1}H NMR (270 MHz, $CDCl_3$): δ = 4.02-3.88 (3H, m), 3.69 (1H, br, C10-H), 3.62 (1H, dd, J = 9.5, 4.6 Hz, C12-H), 3.58-3.32 (3H, m, C17-H and C18-H_2), 3.51 (3H, s, OMe), 3.41 (3H, s, OMe), 3.38 (3H, s, OMe), 2.79 (1H, d, J = 9.3 Hz, C13-H), 1.70-1.50 (1H, br, OH), 1.68 (2H, t, J = 6.4 Hz, C16-H_2), 0.972 (3H, t, J = 8.3 Hz, CH_3CH_2), 0.970 (6H, t, J = 8.0 Hz, CH_3CH_2), 0.92 (3H, s, C14-Me), 0.87 (3H, s, C14-Me), 0.626 (4H, q, J = 7.9 Hz, CH_3CH_2), 0.623 (2H, q, J = 8.0 Hz, CH_3CH_2).

^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 86.7 (1), 78.3 (1), 76.7 (1), 75.8 (2), 72.3 (1), 71.0 (1), 62.5 (3), 59.1 (3), 57.3 (3), 57.1 (2), 41.3 (0), 31.2 (2), 23.2 (3), 13.7 (3), 6.8 (3, 3C), 6.0 (2), 4.9 (2, 2C).

LRMS m/z (CI, NH_3) 407 [$(M+H)^+$, 80], 377 (50), 345 (30), 213 (100).

Microanalysis: Anal. Calcd for $C_{20}H_{42}O_6Si$: C, 59.11; H, 10.34. Found: C, 59.06; H, 10.17.

(2*S*,3*R*,4*S*,6*R*)-2-Formyl-4-methoxy-6-[(2*S*)-2,3-dimethoxypropyl]-5,5-dimethyl-3-(triethylsilyloxy)-tetrahydro-2*H*-pyran 5.20.

5.19
$C_{20}H_{42}O_6Si$
Mol. Wt.: 406.63

5.20
$C_{20}H_{40}O_6Si$
Mol. Wt.: 404.63

Dess-Martin periodinane was added in one portion to a solution of the alcohol **5.19** (200 mg, 0.49 mmol) in CH_2Cl_2 (8 mL) at room temperature. After 40 min the reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (20 mL). After stirring for 10 min the organic layer was removed and the aqueous layer extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated to give crude aldehyde **5.20** as a colourless oil (100%). Due to its instability, the aldehyde **5.20** was used immediately in next step. Analytical data was collected without further purification.

$[\alpha]_D^{20}$ +29.2 (c 1.7, $CHCl_3$).

ν_{max} film/cm^{-1} 1729 (s), 1604 (s).

^{1}H NMR (270 MHz, $CDCl_3$): δ = 10.1 (1H, s, C10-H), 4.31 (1H, d, J = 7.3 Hz, C11-H), 4.14 (1H, dd, J = 9.7, 7.1 Hz, C12-H), 3.72-3.56 (3H, m, C17-H, C18-H_2), 3.52 (3H, s, OMe), 3.51 (1H, dd, J = 9.6, 2.7 Hz, C15-H), 3.43 (3H, s, OMe), 3.40 (3H, s, OMe), 2.64 (1H, d, J = 9.7 Hz, C13-H), 1.70-1.50 (2H, m, C16-H_2), 1.00 (9H, t, J = 8.3 Hz, CH_3CH_2), 0.89 (3H, s, C14-Me), 0.85 (3H, s, C14-Me), 0.696 (4H, q, J = 7.9 Hz, CH_3CH_2), 0.692 (2H, q, J =7.9 Hz, CH_3CH_2).

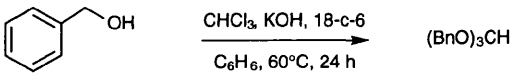
^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 202.8 (1), 88.1 (1), 80.7 (1), 77.8 (1), 77.0 (1), 72.6 (2), 71.1 (1), 62.3 (3), 59.1 (3), 57.8 (3), 41.4 (0), 29.7 (2), 22.9 (3), 13.6 (3), 6.7 (3, 3C), 4.8 (2, 3C).

LRMS *m/z* (CI) 405 [$(M+H)^+$, 100].

HRMS (CI mode) Found: $(M+H)^+$, 405.2668. $C_{20}H_{41}O_6Si$ requires *M*, 405.2672.

Benzyl orthoformate

Benzyl orthoformate was synthesised according to literature procedure[121].



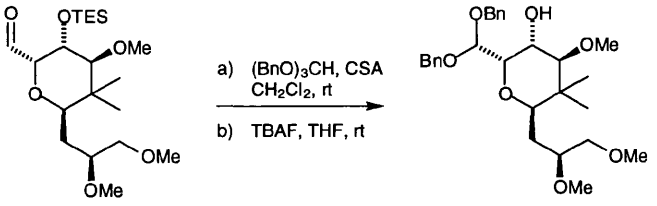
C_7H_8O
Mol. Wt.: 108.14

$C_{22}H_{22}O_3$
Mol. Wt.: 334.41

Powdered KOH (13 g) was added to an ice cooled solution of benzyl alcohol (24 mL), chloroform (6 mL), 18-crown-6 (300 mg) in benzene (100 mL). The mixture was heated at 60°C (temp. of oil bath) over 24 h, filtered through a pad of celite and concentrated then again filtered and excess benzyl alcohol was removed by Kugelrohr distillation (150°C 0.01 mm Hg). The residue was filtered through a pad of silica (2 g, toluene:NEt_3 5%) and heated on high vacuum to give yellow-brown residue of benzyl orthoformate (3.77 g, 16.6%).

^{13}C NMR Spectroscopic data was in agreement with that reported in the literature[99].

(2*S*,3*R*,4*S*,6*R*)-2-Dibenzyloxymethyl-4-methoxy-6-[(2*S*)-2,3-dimethoxypropyl]-5,5-dimethyl-tetrahydro-2*H*-pyran-3-ol 5.21.



5.20
$C_{20}H_{40}O_6Si$
Mol. Wt.: 404.63

5.21
$C_{28}H_{40}O_7$
Mol. Wt.: 488.61

A solution of aldehyde **5.20** (891 mg, 2.19 mmol), benzyl orthoformate (2.22 g, 6.6 mmol) and camphorsulfonic acid (109 mg, 0.43 mmol) in CH_2Cl_2 (10 mL) was stirred at room temperature for 5 h. Solid potassium carbonate (138 mg) was added and the solvent removed *in vacuo*. The residue was taken up in THF (20 mL) to which TBAF (3.15 g, 10 mmol) was added and the mixture was stirred at room temperature. After 11 h the reaction mixture was concentrated and the residue was taken up in Et_2O (150 mL), washed with water (2 x 50 mL) and brine. The organic phase was dried (Na_2SO_4) and concentrated. The residue was purified by column

chromatography (SiO_2 30 g, hexanes:Et_2O 10-80%) to give hydroxy acetal **5.21** (908 mg, 90%) as a yellow oil: $[\alpha]_D^{20}$ +89.6 (*c* 1.6, $CHCl_3$).

ν_{max} film/cm^{-1} 3452 (br).

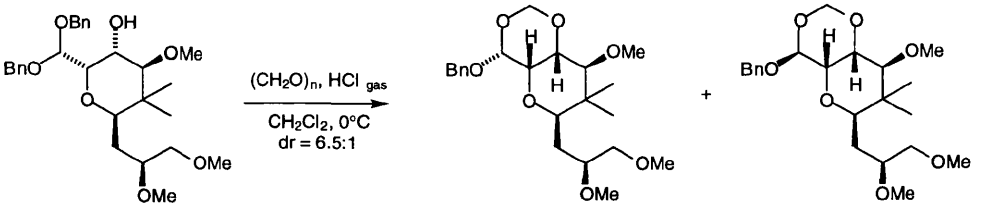
^1H NMR (360 MHz, $CDCl_3$, 333K): δ= 7.45-7.25 (10H, m), 5.11 (1H, d, *J* = 5.3 Hz, C10-H), 4.78 (1H, d, *J* = 11.6 Hz), 4.77 (1H, d, *J* = 11.6 Hz), 4.72 (1H, d, *J* = 11.6 Hz), 4.65 (1H, d, *J* = 11.6 Hz), 4.16 (1H, t, *J* = 5.5 Hz, C11-H), 4.04-3.95 (1H, m, C12-H), 3.57 (1H, dd, *J* = 10.5, 2.2 Hz, C15-H) 3.52-3.36 (3H, m, C17-H, C18-H_2), 3.50 (3H, s, OMe), 3.31 (3H, s, OMe), 3.29 (3H, s, OMe), 2.99 (1H, d, *J* = 8.1 Hz, C13-H), 2.80 (1H, d, *J* = 4.6 Hz, OH), 1.76 (1H, ddd, *J* = 14.5, 10.5, 3.1 Hz, C16H_AH_B), 1.66 (1H, ddd, *J* = 14.3, 8.8, 2.2 Hz, C16H_AH_B), 0.97 (3H, s, C14-Me), 0.90 (3H, s, C14-Me).

^{13}C NMR (90 MHz, $CDCl_3$, 333K): δ= 138.2 (0), 137.5 (0), 128.8 (1), 128.6 (1), 128.3 (1, 2C), 128.2 (1, 2C), 127.9 (1, 4C), 101.4 (1), 87.3 (1), 78.3 (1), 77.5 (1), 73.6 (2), 72.6 (1), 70.4 (2), 69.8 (1), 68.3 (2), 61.7 (3), 59.3 (3), 57.0 (3), 40.1 (0), 30.1 (2), 24.8 (3), 16.0 (3).

LRMS *m/z* (CI, NH_3) 506 [$(M+NH_4)^+$, 2%], 489 [$(M+H)^+$, 0.4], 398 (0.8), 381 (0.8).

HRMS (CI mode) [Found: $(M+H)^+$, 489.2859. $C_{28}H_{41}O_7$ requires *M*, 489.2852.

(1*R*,5*S*,6*S*,8*R*,10*S*)-5-Benzyloxy-8-[(2*S*)-2,3-dimethoxypropyl]-9,9-dimethyl-10-methoxy-2,4,6-trioxabicyclo[4,4,0]decane 5.22a and (1*R*,5*R*,6*S*,8*R*,10*S*)-5-Benzyloxy-8-[(2*S*)-2,3-dimethoxypropyl]-9,9-dimethyl-10 methoxy-2,4,6-trioxabicyclo[4,4,0]decane 5.22b.



5.21
$C_{28}H_{40}O_7$
Mol. Wt.: 488.61

5.22a
$C_{22}H_{34}O_7$
Mol. Wt.: 410.50

5.22b
$C_{22}H_{34}O_7$
Mol. Wt.: 410.50

HCl gas was passed through a stirred mixture of hydroxy acetal **5.21** (908 mg, 1.97 mmol) and paraformaldehyde (635 mg, 21.2 mmol) in CH_2Cl_2 (80 mL) at 0°C for 30 min. The white suspension of paraformaldehyde disappeared to give a colourless solution. A stream of nitrogen was then passed through the reaction mixture for 1 h to form a white suspension. The mixture was poured onto saturated aqueous $NaHCO_3$, the organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 25 mL). The combined extracts were dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography (SiO_2 13g, hexanes:Et_2O 5-40%) to give the acetals **5.22a,b** (740 mg, 93%) as a 6.5:1 mixture of diastereoisomers according to integration of the C-10 methine doublets at δ= 5.15 (major) and 5.25 (minor) revealed in the ^1H

NMR spectrum ($CDCl_3$). For analysis a sample of the acetals **5.22a,b** were separated by column chromatography (SiO_2, hexanes:Et_2O 5-30%).

Major diastereoisomer **5.22a**:

$[\alpha]_D^{20}$ +32.3 (*c*0.7, $CHCl_3$).

ν_{max} film/cm^{-1} 2879 (s), 1455 (s), 1178 (s), 1101 (s), 1044 (s), 981 (s), 821 (s), 735 (s), 700 (s).

^1H NMR (270 MHz, $CDCl_3$): δ = 7.40-7.27 (5H, m), 5.15 (1H, d, J = 6.0 Hz, OCH_AH_BO), 4.86 (1H, d, J = 6.0 Hz, OCH_AH_BO), 4.85 (1H, s, C10-H), 4.81 (1H, d, J = 12.0 Hz, $PhCH_2$), 4.58 (1H, d, J = 11.8 Hz, $PhCH_2$), 3.94 (1H, t, J = 2.7 Hz, C12-H), 3.71 (1H, t, J = 1.7 Hz, C11-H), 3.57 (1H, dd, J = 12.2, 3.1 Hz, C15-H), 3.56-3.40 (2H, m, C18-H_2), 3.40-3.30 (1H, m, C17-H), 3.38 (3H, s, OMe), 3.33 (3H, s, OMe), 3.30 (3H, s, OMe), 2.89 (1H, d, J = 3.1 Hz, C13-H), 2.28 (1H, ddd, J = 15.3, 12.4, 4.6 Hz, C16-H_AH_B), 1.59 (1H, ddd, J = 14.9, 7.7, 3.1 Hz, C16-H_AH_B), 1.22 (3H, s, C14-Me), 0.91 (3H, s, C14-Me).

^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 137.2 (0), 128.6 (1, 2C), 128.2 (1, 2C), 128.0 (1), 96.7 (1), 85.3 (2), 83.8 (1), 78.7 (1), 78.5 (1), 73.5 (2), 70.1 (1), 69.1 (2), 63.1 (1), 59.6 (3), 59.3 (3), 57.2 (3), 37.0 (0), 28.4 (2), 27.4 (3), 21.8 (3).

LRMS *m/z* (CI, NH_3) 411 [$(M+H)^+$, 45], 307 (50), 345 (25), 277 (65), 126 (100).

Microanalysis: Anal. Calcd for $C_{22}H_{34}O_7$: C, 64.39; H, 8.29. Found: C, 64.16; H, 8.47.

Minor diastereoisomer **5.22b**:

$[\alpha]_D^{20}$ +11.4° (*c* 0.8, $CHCl_3$).

ν_{max} film/cm^{-1} 2879 (s), 1455 (s), 1178 (s), 1101 (s), 1044 (s), 981 (s), 821 (s), 735 (s), 700 (s).

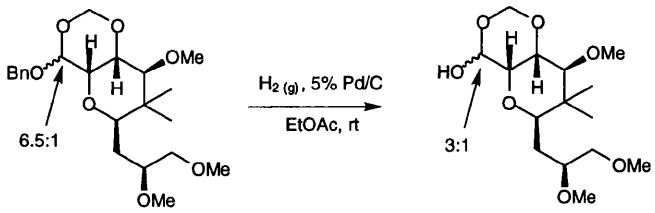
^1H NMR (360 MHz, $CDCl_3$, 333 K): δ = 7.40-7.27 (5H, m), 5.24 (1H, d, J = 6.3 Hz, OCH_AH_BO), 5.00 (1H, d, J = 3.6 Hz, C10-H), 4.89 (1H, d, J = 11.8 Hz, $PhCH_2$), 4.63 (1H, d, J = 6.3 Hz, OCH_AH_BO), 4.60 (1H, d, J = 11.8 Hz, $PhCH_2$), 4.11 (1H, dd, J = 6.1, 3.6 Hz, C12-H), 4.03 (1H, dd, J = 10.2, 2.5 Hz), 3.98 (1H, dd, J = 18.8, 6.1 Hz), 3.50-3.20 (3H, m), 3.50 (3H, s, OMe), 3.39 (1H, d, J = 2.4 Hz, C13-H), 3.34 (3H, s, OMe), 3.20 (3H, s, OMe), 1.74-1.56 (2H, m, C16-H_2), 0.99 (3H, s, C14-Me), 0.87 (3H, s, C14-Me).

^{13}C NMR (90 MHz, $CDCl_3$, 333 K): δ = 137.5 (0), 128.7 (1, 2C), 128.1 (1, 2C), 128.0(1), 99.0 (1), 82.2 (2), 81.9 (1), 78.5 (1), 76.8 (1), 74.2 (2), 73.6 (1), 70.4 (2), 67.3 (1), 61.2 (3), 59.2 (3), 57.1 (3), 40.2 (0), 30.4 (2), 24.5 (3), 15.2 (3).

LRMS *m/z* (CI, NH_3) 411 [$(M+H)^+$, 45], 307 (15), 294 (20), 277 (35), 126 (100), 91 (70).

Microanalysis: Anal. Calcd for $C_{22}H_{34}O_7$: C, 64.39; H, 8.29. Found: C, 64.22; H, 8.41.

(1*R*,5*RS*,6*R*,8*R*,10*S*)-10-Methoxy-8-[(2*S*)-2,3-dimethoxy-propyl]-9,9-dimethyl-2,4,7-trioxabicyclo[4.4.0]decan-5-ol 5.23.



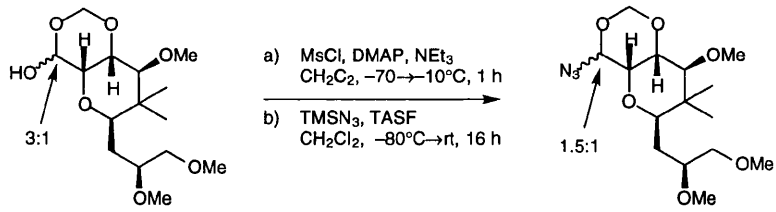
5.22a,b
$C_{22}H_{34}O_7$
Mol. Wt.: 410.50

5.23
$C_{15}H_{28}O_7$
Mol. Wt.: 320.38

To a solution of acetals **5.22a,b** (400 mg, 0.97 mmol) in EtOAc (30 mL) was added Pd/C 5% (760 mg). The argon atmosphere was replaced with hydrogen and the mixture was stirred vigorously for 17 h. The hydrogen gas was removed and the mixture filtered through a pad of celite and concentrated. The residue was passed through a pad of silica (7 g, hexanes:EtOAc 50%) to give a 3:1 mixture hemiacetals **5.23** (271 mg, 0.844 mmol, 87%) according to integration of the C14-Me singlets at $\delta = 0.91$ (major) and 0.94 (minor) revealed in the ^1H NMR spectrum ($CDCl_3$) of the mixture.

^1H and ^{13}C NMR spectroscopic data were in agreement with that reported in the literature[17].

Formation of azides 5.24.

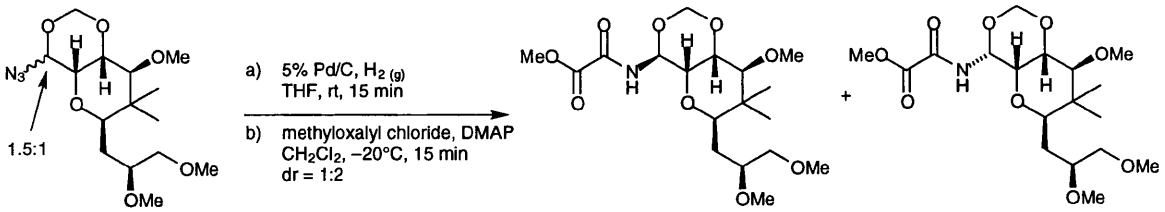


5.23
$C_{15}H_{28}O_7$
Mol. Wt.: 320.38

5.24
$C_{15}H_{27}N_3O_6$
Mol. Wt.: 345.39

As previously reported in 74% yield[17].

Formation of oxalamides 1.57a and 1.57b.



5.24
$C_{15}H_{27}N_3O_6$
Mol. Wt.: 345.39

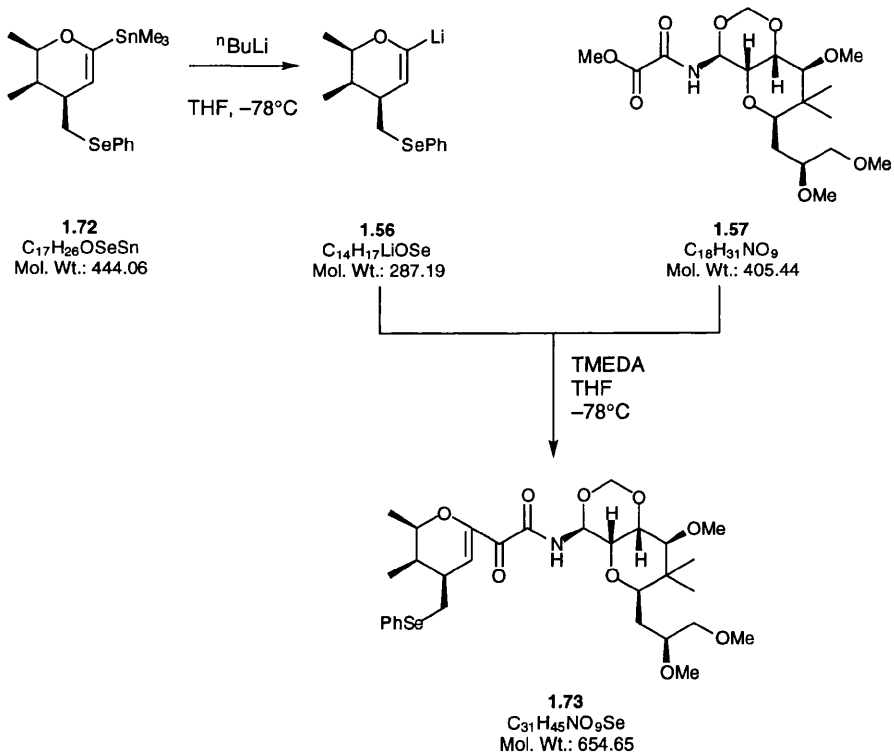
1.57
$C_{18}H_{31}NO_9$
Mol. Wt.: 405.44

1.71
$C_{18}H_{31}NO_9$
Mol. Wt.: 405.44

As previously reported in 57% yield[17].

(1*S*,5*S*,6*S*,8*S*,10*R*)-5{[(2*R*,3*R*,4*R*)-3,4-dihydro-2,3-dimethyl-4-phenylselenylmethyl-2*H*-pyran-6-yl]-oxoethanamido}-8-[(2*S*)-2,3-dimethoxypropyl]-9,9-dimethyl-10-methoxy-2,4,7-trioxabicyclo[4.4.0]decane 1.73.

Prepared according to literature procedure[17].



1.72
$C_{17}H_{26}OSeSn$
Mol. Wt.: 444.06

1.56
$C_{14}H_{17}LiOSe$
Mol. Wt.: 287.19

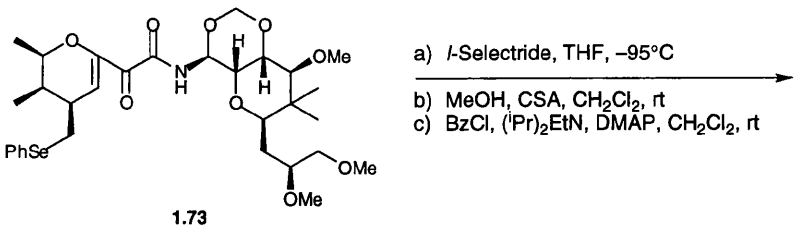
1.57
$C_{18}H_{31}NO_9$
Mol. Wt.: 405.44

1.73
$C_{31}H_{45}NO_9Se$
Mol. Wt.: 654.65

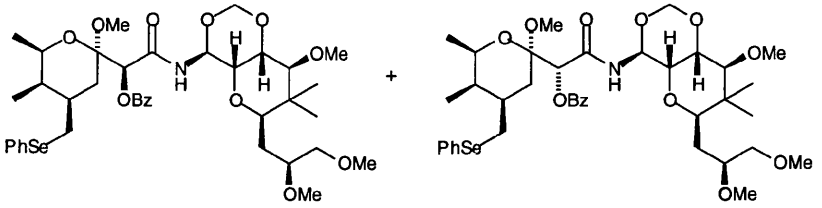
^{n}BuLi (1.5 M in hexanes, 0.375 mL, 0.562 mmol) was added dropwise to a stirred solution of vinyl stannane **1.72** (256 mg, 0.576 mmol) in THF (2.7 mL) at -80°C. The solution was stirred for 15 min and TMEDA (0.1 mL, 0.66 mmol) was added. After 10 min a cold (-80°C) solution of ester **1.57** (72 mg, 0.18 mmol) in THF (1 + 0.5 + 0.5 mL) was quickly added *via* cannula. The reaction mixture was stirred for 30 min, treated with brine and extracted with CH_2Cl_2 (3 x 20 mL). The combined extracts were dried (Na_2SO_4) and concentrated. The

residue was purified by column chromatography (SiO_2 4 g, hexanes:EtOAc) to give enone **1.73** (87 mg, 74%) as a colourless oil. ^1H and ^{13}C NMR data were in agreement with literature[36].

Formation of benzoates 1.74a and 1.74b



1.73
$C_{31}H_{45}NO_9Se$
Mol. Wt.: 654.65



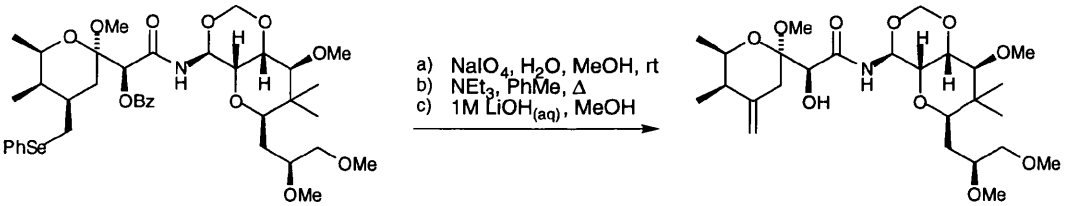
1.74a
$C_{39}H_{55}NO_{11}Se$
Mol. Wt.: 792.81

dr = 3:1

1.74b
$C_{39}H_{55}NO_{11}Se$
Mol. Wt.: 792.81

As previously reported in 55% overall yield.[17]

18-*O*-Methyl Mycalamide B 1.5



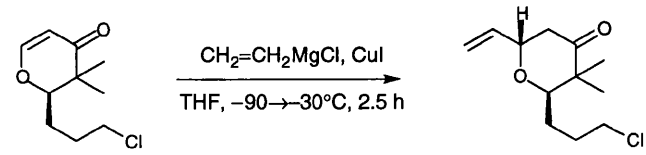
1.74a
$C_{39}H_{55}NO_{11}Se$
Mol. Wt.: 792.81

1.5 18-*O*-methyl mycalamide B
$C_{26}H_{45}NO_{10}$
Mol. Wt.: 531.64

As previously reported in 68% yield.[17]

7.3 Synthesis of Theopederin D

(2*S*,6*R*)-6-(3-Chloropropyl)-tetrahydro-5,5-dimethyl-2-vinyl-2*H*-pyran-4-one 6.1.



2.2
$C_{10}H_{15}ClO_2$
Mol. Wt.: 202.68

6.1
$C_{12}H_{19}ClO_2$
Mol. Wt.: 230.73

To a stirred solution of enone **2.2** (14.2 g, 70.1 mmol) and copper(I) iodide (700 mg, 3.7 mmol) in THF (120 mL) at -95°C was added a solution of vinyl magnesium chloride (1.7 M in THF, 60 mL, 102 mmol) over 30 min. The reaction mixture was stirred for 1.5 h at –90°C and then allowed to warm up to -30°C over 1.5 h. After such time saturated aqueous NH_4Cl (200 mL) was added followed by concentrated ammonia solution (40 mL). The resulting mixture was stirred for 30 min at room temperature before being extracted with Et_2O (3 x 60 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was purified by Kugelrohr distillation to give vinyl ketone **6.1** (12.69 g, 55.3 mmol, 79%) as a colourless oil: bp 160-180°C at 0.07 mm Hg. The diastereomeric ratio was found to be 15:1 from the ^1H NMR spectrum by integration of the two doublet of doublet signals derived from C12-H_2 [^1H NMR (360 MHz, $CDCl_3$): δ = 2.85 and 2.81 (minor) and 2.55 and 2.67 ppm (major) ppm].

$[\alpha]_D^{20}$ +46.5 (*c* 1.1, $CHCl_3$).

ν_{max} film/cm^{-1} 1712 (s), 1128 (s).

^1H NMR (400 MHz, $CDCl_3$): δ = 5.85 (1H, ddd, *J* = 17.2, 11.2, 4.8 Hz, C10-H), 5.25 (1H, t, *J* = 1.2, C9-$H_A$$H_B$), 5.21 (1H, dt, *J* = 8.8, 1.2 Hz, C9-$H_A$$H_B$), 4.56 (1H, qt, *J* = 4.8, 1.6 Hz, C11-H), 3.61 (1H, dd, *J* = 10.0, 3.6 Hz, C15-H), 3.55 (2H, t, *J* = 6.4 Hz, C18-H_2), 2.67 (1H, dd, *J* = 14.4, 6.0 Hz, C12-$H_A$$H_B$), 2.55 (1H, dd, *J* = 14.4, 6.0 Hz, C12-$H_A$$H_B$), 2.02-1.92 (1H, m), 1.81-1.70 (1H, m), 1.70-1.50 (2H, m), 1.11 (3H, s, C14-Me), 1.06 (3H, s, C14-Me).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 211.5 (0), 137.3 (1), 117.9 (2), 79.3 (1), 72.6 (1), 49.8 (0), 45.0 (2), 41.5 (2), 29.3 (2), 25.9 (2), 22.0 (3), 19.4 (3).

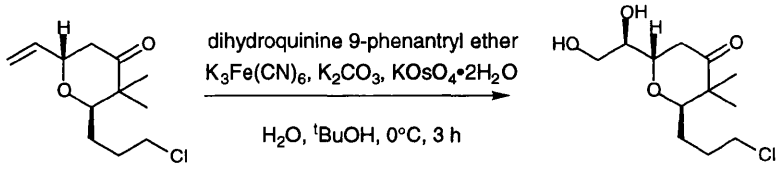
LRMS *m/z* (CI) 248 [$(M+NH_4)^+$, 100%].

HRMS (CI) Found: $(M+H)^+$, 230.1071. $C_{12}H_{19}ClO_2$ requires *M*, 230.1074.

Microanalysis: Anal. Calcd for $C_{12}H_{19}ClO_2$: C,62.47; H, 8.24. Found: C, 62.48; H, 8.18.

(2*S*,6*R*)-6-(3-Chloropropyl)-5,5-dimethyl-2-[(1*R*)-1,2-dihydroxyethyl]-tetrahydro-2*H*-pyran-4-one 6.2.

The asymmetric dihydroxylation was performed according to literature procedure.[100]



6.1
$C_{12}H_{19}ClO_2$
Mol. Wt.: 230.73

6.2
$C_{12}H_{21}ClO_4$
Mol. Wt.: 264.75

Olefin **6.1** (10.0 g, 43.5 mmol) and hydroqinine 9-phenanthryl ether **6.4** (439 mg, 0.88 mmol) were stirred in ^tBuOH (260 mL) until the ligand dissolved before water (260 mL), $K_3Fe(CN)_6$ (43.3 g, 131.3 mmol) and K_2CO_3 (18.3 g, 132.6 mmol) were added and the mixture was cooled to 0°C. Potassium osmate dihydrate (267 mg, 0.72 mmol) was added. The reaction mixture was stirred for 3 h at 0°C then treated with saturated aqueous Na_2SO_3 (400 mL) and water (100 mL). After stirring at ambient temperature for 0.5 h the mixture was extracted with CH_2Cl_2 (400 mL + 2 x 200 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated to give the crude diol. Filtration through silica gel (100 g, Et_2O:EtOAc 10-40%) afforded diol **6.2** (8.63 g, 32.7 mmol, 75%) as a 13:1 mixture of diastereoisomers as determined from the ^1H NMR spectrum by integration of signals derived from the C14-Me group [^1H NMR (360 MHz, $CDCl_3$): δ = 1.26 ppm (major) and 1.28 ppm (minor)].

$[\alpha]_D^{19}$ –8.0 (*c* 1.1, $CHCl_3$).

ν_{max} film/cm^{-1} 3412 (br), 1712 (s).

^1H NMR (360 MHz, $CDCl_3$): δ = 3.94 (1H, dt, *J* = 9.7, 4.6 Hz, C11-H), 3.81 (1H, ddd, *J* = 9.8, 6.2, 3.7 Hz, C10-H), 3.77 (1H, dd, *J* = 11.9, 3.5 Hz, C15-H), 3.73 (1H, dd, *J* = 11.4, 3.6 Hz, C9-H_AH_B), 3.65 (1H, dd, *J* = 11.3, 6.4 Hz, C9-H_AH_B), 3.57 (2H, t, *J* = 6.0 Hz, C18-H_2), 3.00-2.60 (2H, br, OH), 2.78 (1H, dd, *J* = 14.6, 9.7 Hz, C12-H_AH_B), 2.40 (1H, dd, *J* = 14.6, 4.3 Hz, C12-H_AH_B), 2.00-1.95 (1H, m), 1.80-1.45 (3H, m), 1.27 (3H, s, C14-Me), 1.01 (3H, s, C14-Me).

^{13}C NMR (90 MHz, $CDCl_3$): δ = 212.9 (0), 81.6 (1), 73.6 (1), 71.7 (1), 63.2 (2), 49.6 (0), 44.5 (2), 38.8 (2), 28.7 (2), 25.3 (2), 24.2 (3), 19.3 (3).

LRMS *m/z* (CI) 248 [$(M+NH_4)^+$, 100%].

Microanalysis: Anal. Calcd for $C_{12}H_{21}ClO_4$: C, 54.44; H, 7.94; Cl, 13.42. Found: C, 54.50; H, 7.74; Cl, 13.72.

The following additional experiments were performed on a 20 mg scale:

AD-mix-α

α/β	ca 1:2	(TLC)	reaction slow	abandoned

AD-mix-β

α/β	ca 2:1	(TLC)	reaction slow	abandoned

DHQ 2,5-diphenyl-4,6-pyrimidinediyl diether [$(DHQ)_2PYR$]

α/β	ca 1:3.5

DHQD 2,5-diphenyl-4,6-pyrimidinediyl diether[$(DHQD)_2PYR$]

α/β	ca 2.6:1

DHQ 4-methyl-2-quinoyl ether

α/β	ca 1:7.5

DHQ 9-phenantryl ether

α/β	ca 1:8.1

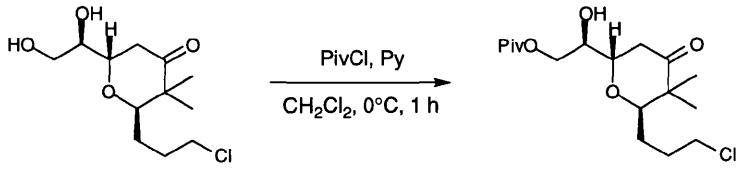
DHQD-PYDZ

α/β	ca 1.3:1

without chiral ligand

α/β	ca 1:1.5	(TLC)	reaction slow	abandoned

(2*S*,6*R*)-6-(3-Chloropropyl)-5,5-dimethyl-2-[(1*R*)-2-(*tert*-butylcarbonyloxy)-1-hydroxyethyl]-tetrahydro-2*H*-pyran-4-one 6.3.



6.2
$C_{12}H_{21}ClO_4$
Mol. Wt.: 264.75

6.3
$C_{17}H_{29}ClO_5$
Mol. Wt.: 348.86

To a solution of diols **6.2** (dr = 13:1, 11.3 g, 43.0 mmol) and pyridine (10.4 mL, 128.9 mmol) in CH_2Cl_2 (70 mL) at 0°C was added pivaloyl chloride (10.8 mL, 87.5 mmol). The reaction mixture was stirred at 0°C for 1 h, treated with saturated aqueous $NaHCO_3$ and extracted with Et_2O (3 x 70 mL). The combined extracts were washed with 2M $HCl_{(aq)}$ (50 mL), brine (70 mL), dried (Na_2SO_4) and concentrated. The residue was filtered

through a pad of silica (100 g, hexanes:Et_2O 20-50%) and concentrated. Diastereoisomerically pure ester **6.3** (11.6 g, 33.5 mmol, 78%) was obtained as colourless needles by recrystallisation from hexanes:Et_2O; mp 69-70°C (hexanes:Et_2O)

$[\alpha]_D^{19}$ –2.0 (*c* 1.0, $CHCl_3$).

ν_{max} CCl_4/cm^{-1} 3599 (br), 1716 (s).

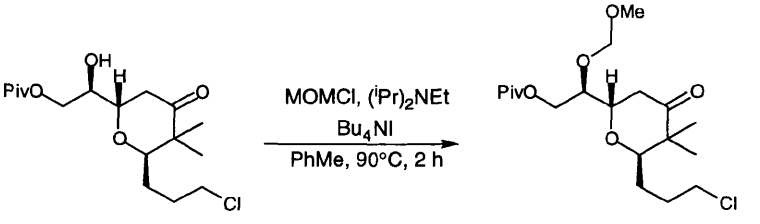
^1H NMR (400 MHz, $CDCl_3$): δ = 4.27 (1H, dd, *J* = 11.6, 3.6 Hz, C9-H_AH_B), 4.12 (1H, dd, *J* = 11.6, 6.4 Hz, C9-H_AH_B), 3.96 (1H, dddd, *J* = 14.8, 6.4, 5.6, 4.0 Hz, C10-H), 3.92 (1H, dt, *J* = 9.8, 5.3 Hz, C11-H), 3.80 (1H, dd, *J* = 12.0, 3.2 Hz, C15-H), 3.60-3.54 (2H, m, C18-H_2), 2.82 (1H, dd, *J* = 14.8, 9.6 Hz, C12-H_AH_B), 2.70-2.20 (1H, d, *J* = 4.4 Hz, OH), 2.42 (1H, dd, *J* = 14.8, 4.0 Hz, C12-H_AH_B), 2.00-1.85 (1H, m), 1.84-1.50 (3H, m), 1.29 (3H, s, C14-Me), 1.22 (9H, s, ^{t}Bu), 1.03 (3H, s, C14-Me).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 211.9 (0), 179.1 (0), 82.1 (1), 72.3 (1), 71.2 (1), 64.9 (2), 49.7 (0), 44.8 (2), 39.1 (0), 38.6 (2), 28.8 (2), 27.4 (3, 3C), 25.4 (2), 24.8 (3), 19.5 (3).

LRMS *m/z* (CI) 349 [$(M+H)^+$, 20%].

Microanalysis: Anal. Calcd for $C_{17}H_{29}ClO_5$: C, 58.54; H, 8.32; Cl, 10.19. Found: C, 58.71; H, 8.02; Cl, 10.37.

(2*S*,6*R*)-6-(3-Chloropropyl)-5,5-dimethyl-2-[(1*R*)-2-(*tert*-butylcarbonyloxy)-1-(methoxymethoxy)ethyl]-tetrahydro-2*H*-pyran-4-one 6.5.



6.3
$C_{17}H_{29}ClO_5$
Mol. Wt.: 348.86

6.5
$C_{19}H_{33}ClO_6$
Mol. Wt.: 392.91

A mixture of alcohol **6.3** (2.4 g, 6.9 mmol), *N*-ethyldiisopropylamine (3.7 mL, 21.1 mmol), tetabutylammonium iodide (128 mg, 0.35 mmol), chloromethyl methyl ether (1.6 mL, 21.1 mmol) and anhydrous toluene (20 mL) were stirred at 90°C for 2 hours. The reaction mixture was cooled to room temperature and treated with saturated aqueous $NaHCO_3$ (30 mL). The layers were separated and the aqueous layer was extracted with Et_2O (2 x 30 mL). The combined organic extracts were washed with brine (30 mL), dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography (SiO_2 25g, hexanes:Et_2O 10-40%) to give MOM ether **6.5** (2.63 g, 6.7 mmol, 97%) as a white solid; mp 42-43°C (hexanes:Et_2O)

$[\alpha]_D^{21}$ +3.4 (*c* 1.4, $CHCl_3$).

ν_{max} CCl_4/cm^{-1} 1732 (s), 1716 (s), 1154 (s).

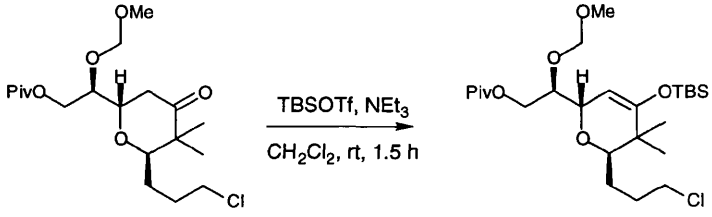
^1H NMR (400 MHz, $CDCl_3$): δ = 4.73 (1H, d, *J* = 6.8 Hz, OCH_AH_BO), 4.64 (1H, d, *J* = 6.8 Hz, OCH_AH_BO), 4.32 (1H, dd, *J* = 12.0, 4.4 Hz, C9-H_AH_B), 4.02 (1H, dd, *J* = 12.0, 5.2 Hz, C9-H_AH_B), 3.95 (1H, dt, *J* = 10.0, 4.4 Hz, C11-H), 3.82 (1H, q, *J* = 4.8 Hz, C10-H), 3.72 (1H, dd, *J* = 11.6, 3.2 Hz, C15-H), 3.51 (2H, t, *J* = 6.0 Hz, C18-H_2), 3.34 (3H, s, OMe), 2.75 (1H, dd, *J* = 14.4, 9.6 Hz, C12-H_AH_B), 2.38 (1H, dd, *J* = 14.4, 4.4 Hz, C12-H_AH_B), 1.95-1.83 (1H, m), 1.78-1.43 (3H, m), 1.23 (3H, s, C14-Me), 1.15 (9H, s, ^tBu), 0.97 (3H, s, C14-Me).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 211.7 (0), 178.1 (0), 96.5 (2), 81.8 (1), 76.7 (1), 70.6 (1), 62.7 (2), 56.1 (3), 49.6 (0), 44.7 (2), 39.0 (2), 38.8 (0), 28.6 (2), 27.2 (3, 3C), 25.2 (2), 24.6 (3), 19.4 (3).

LRMS *m/z* (CI) 393 [$(M+H)^+$, 7%].

Microanalysis: Anal. Calcd for $C_{19}H_{33}ClO_6$: C, 58.09; H, 8.41; Cl, 9.04. Found: C, 58.36; H, 8.12; Cl, 8.94.

(2*S*,6*R*)-4-[(*tert*-Butyldimethylsilyl)oxy]-2-[(1*R*)-2-(*tert*-butylcarbonyloxy)-1-(methoxymethoxy)ethyl]-6-(3-chloropropyl)-5,6-dihydro-5,5-dimethyl-2*H*-pyran 6.6.



6.5
$C_{19}H_{33}ClO_6$
Mol. Wt.: 392.91

6.6
$C_{25}H_{47}ClO_6Si$
Mol. Wt.: 507.18

To a mixture of ketone **6.5** (6.81 g, 17.4 mmol) and triethylamine (4.7 mL, 3.41 g, 33.7 mmol) in CH_2Cl_2 (26 mL) at 0°C was added TBSOTf (4.7 mL, 5.41 g, 20.5 mmol) in a dropwise fashion over 5 min. After the addition was complete the cool bath was removed and the reaction mixture stirred for 1.5 h at ambient temperature. After such time saturated aqueous $NaHCO_3$ (100 mL) was added and the mixture extracted with hexanes (3 x 50 mL). The combined extracts were dried (Na_2SO_4) and concentrated to give crude silyl enol ether **6.6**. TBSOH was removed under vacuum at 50°C, 1 mm Hg overnight to give silyl enol ether **6.6** (8.58 g, 17.0 mmol, 98%) as a clear colourless oil.

For analysis a sample (200 mg) was removed and purified by column chromatography (SiO_2, hexanes:Et_2O 2%).

$[\alpha]_D^{17}$ +10.3 (*c* 1.1, $CHCl_3$).

ν_{max} film/cm^{-1} 1732 (s), 1664 (s), 1154 (s).

^1H NMR (400 MHz, $CDCl_3$): δ = 4.77 (1H, d, *J* = 3.2 Hz, C12-H), 4. 75 (1H, d, *J* = 6.4 Hz, OCH_AH_BO), 4.69 (1H, d, *J* = 6.8 Hz, OCH_AH_BO), 4.50 (1H, dd, *J* = 12.0, 2.4 Hz, C9-H_AH_B), 4.23 (1H, dd, *J* = 7.6, 2.8 Hz, C11-H), 4.11 (1H, dd, *J* = 12.0, 5.6 Hz, C9-H_AH_B), 3.73 (1H, ddd, *J* = 8.0, 6.0, 2.8 Hz, C10-H), 3.65-3.53 (2H, m, C18-H_2), 3.42 (1H, dd, *J* = 10.8, 2.4 Hz, C15-H), 3.40 (3H, s, OMe), 2.10-2.00 (1H, m), 1.84-1.50 (3H, m), 1.22 (9H, s, ^{t}BuCOO), 1.04 (3H, s, C14-Me), 0.96 (3H, s, C14-Me), 0.95 (9H, s, ^{t}BuSi), 0.18 (3H, s, MeSi), 0.18 (3H, s, MeSi).

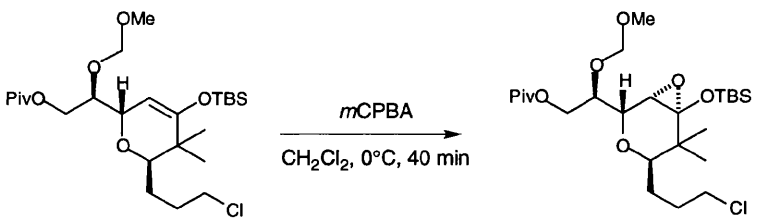
^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.6 (0), 156.3 (0), 98.4 (1), 96.6 (2), 79.2 (1), 77.5 (1), 70.2 (1), 64.4 (2), 56.0 (3), 45.5 (2), 39.0 (0), 38.7 (0), 29.9 (2), 27.4 (3, 3C), 26.3 (2,), 25.9 (3, 3C), 23.3 (3), 19.9 (3), 18.4 (0), -4.2 (3), -4.6 (3).

LRMS *m/z* (CI, NH_3) 524 [$(M+NH_4)^+$, 40%].

HRMS (CI) Found: $(M+H)^+$, 507.2910. $C_{25}H_{48}ClO_6Si$ requires *M*, 507.2909.

Microanalysis: Anal. Calcd for $C_{25}H_{47}ClO_6Si$: C, 59.35; H, 9.23. Found: C, 59.31; H, 9.01.

(2*R*,3*S*,4*S*,6*R*)-4-[(*tert*-Butyldimethylsilyl)oxy]-2-[(1*R*)-2-(*tert*-butylcarbonyloxy)-1-(methoxymethoxy)ethyl]-6-(3-chloropropyl)-3,4-epoxy-tetrahydro-5,5-dimethyl-2*H*-pyran 6.7.



6.6
$C_{25}H_{47}ClO_6Si$
Mol. Wt.: 507.18

6.7
$C_{25}H_{47}ClO_7Si$
Mol. Wt.: 523.17

A solution of *m*-chloroperbenzoic acid (15.2 g, 57-80% from Aldrich) in CH_2Cl_2 (150 mL) was dried over Na_2SO_4, filtered and stirred with sodium hydrogen orthophosphate (11.2 g, 78.7 mmol) at room temperature for 30 min. The mixture was then cooled to 0°C and a solution of enol ether **6.6** (8.58 g, 17.0 mmol) in CH_2Cl_2 (30 + 8 + 8 mL) was added dropwise over 20 min. The reaction mixture was stirred for 40 min, treated with saturated aqueous Na_2SO_3 and hexanes (500 mL). The phases were separated. The organic phase was extracted with 2M $NaOH_{(aq)}$ (2 x 70 mL), washed with water (70 mL), brine (70 mL), dried (Na2SO4) and concentrated to afford crude epoxide **6.7** (9.58g, 18.4 mmol, 108%) as a single diastereoisomer and a clear colourless oil.

For analysis a sample (200 mg) was removed and purified by column chromatography (SiO_2, hexanes:Et_2O 2%).

$[\alpha]_D^{20}$ +10.0 (*c* 2.0, $CHCl_3$).

ν_{max} film/cm^{-1} 1732 (s), 1152 (s).

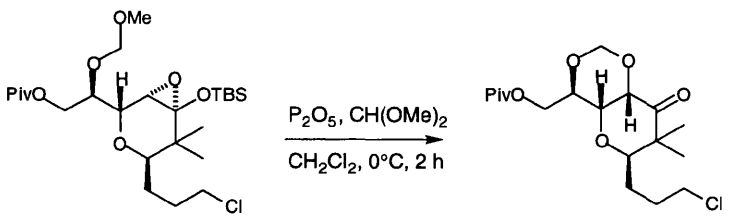
^1H NMR (360 MHz, $CDCl_3$): δ = 4.78 (1H, d, *J* = 6.7 Hz, OCH_AH_BO), 4.74 (1H, d, *J* = 6.7 Hz, OCH_AH_BO), 4.54 (1H, dd, *J* = 12.0, 1.8 Hz, C9-H_AH_B), 4.05 (1H, dd, *J* = 9.9, 3.2 Hz, C11-H), 4.01 (1H, dd, *J* = 12.0, 4.3 Hz, C9-H_AH_B), 3.94 (1H, ddd, *J* = 9.9, 4.1, 1.6 Hz, C10-H), 3.57-3.47 (2H, m, C18-H_2), 3.51 (1H, d, *J* = 3.2 Hz, C12-H), 3.43 (3H, s, OMe), 3.27 (1H, dd, *J* = 10.3, 1.4 Hz, C15-H), 1.22 (9H, s, ^{t}BuCOO), 1.05 (3H, s, C14-Me), 0.98 (3H, s, C14-Me), 0.91 (9H, s, ^{t}BuSi), 0.14 and 0.06 (3H each, s, Me_2Si).

^{13}C NMR (90 MHz, $CDCl_3$): δ = 178.5 (0), 96.3 (2), 86.6 (0), 76.0 (1), 71.7 (1), 68.9 (1), 63.6 (2), 60.4 (1), 56.2 (3), 45.3 (2), 39.1 (0), 38.9 (0), 30.1 (2), 27.4 (3, 3C), 26.9 (2), 25.8 (3, 3C), 18.7 (3), 18.0 (0), 16.8 (3), -3.1 (3), -3.4 (3).

LRMS *m/z* (CI, NH_3) 540 [$(M+NH_4)^+$, 100%].

HRMS (EI) Found: $(M+H)^+$, 522.2781. $C_{25}H_{47}ClO_7Si$ requires *M*, 522.2780.

(1*S*,5*R*,6*R*,8*R*)-5-(*tert*-Butylcarbonyloxy)methyl-8-(3-chloropropyl)-9,9-dimethyl-2,4,7-trioxabicyclo[4,4,0]decan-10-one 6.10.



6.7
$C_{25}H_{47}ClO_7Si$
Mol. Wt.: 523.17

6.10
$C_{18}H_{29}ClO_6$
Mol. Wt.: 376.87

A mixture of crude epoxide **6.7** (3.5 g, 92% pure, 6.17 mmol) from above experiment in CH_2Cl_2 (10 +5 mL) was added to an ice cold solution of dimethoxymethane (30 mL) and P_2O_5 (2.5 g) in CH_2Cl_2 (15 mL) over 5 min. The cool bath was removed and the reaction mixture was stirred at ambient temperature for 2 h. After such time the reaction mixture was poured onto saturated aqueous $NaHCO_3$ (50 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 100 mL). The combined extracts were washed with brine (100 mL), dried (Na_2SO_4) and concentrated. ^1H NMR spectrum of crude product showed a 15:1 ratio of diastereoisomers by integration of signals derived from C14-Me group [^1H NMR (360 MHz, $CDCl_3$): δ = 1.06 ppm (major) and 1.32 ppm (minor)]. The crude product was purified by column chromatography (SiO_2 45 g,

hexanes:Et_2O 10-40%) to give ketone **6.10** (1.79 g, 4.75 mmol, 77% over 3 steps) as a white solid: mp 88-89°C (hexanes:Et_2O).

$[\alpha]_D^{20}$ +166.6 (*c* 1.4, $CHCl_3$).

ν_{max} KBr/cm^{-1} 1724 (s) 1282 (m), 1164 (s), 1150 (s).

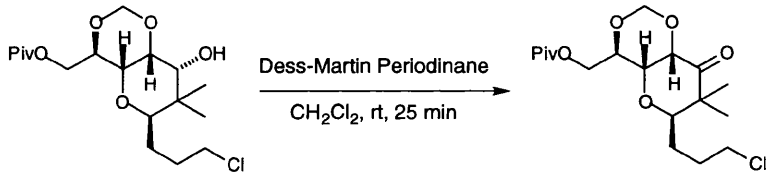
^1H NMR (400 MHz, $CDCl_3$): δ = 4.91 (1H, d, J = 7.6 Hz, C12-H), 4.83 (1H, d, J = 6.8 Hz, OCH_AH_BO), 4.80 (1H, d, J = 6.4 Hz, OCH_AH_BO), 4.46 (1H, dd, J = 12.4, 1.6 Hz, C9-H_AH_B), 4.27 (1H, dd, J = 10.8, 7.6 Hz, C11-H), 4.00 (1H, dd, J = 12.0, 6.8 Hz, C9-H_AH_B), 3.86 (1H, ddd, J = 10.8, 7.2, 1.2 Hz, C10-H), 3.67-3.55 (2H, m, C18-H_2), 3.54 (1H, dd, J = 12.4, 4.0 Hz, C15-H), 2.10-2.00 (1H, m), 1.85-1.75 (1H, m), 1.65-1.56 (2H, m), 1.19 (12H, s, ^{t}BuCOO and C14-Me), 1.05 (3H, s, C14-Me).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 208.6 (0), 178.7 (0), 90.3 (2), 79.0 (1), 73.8 (1), 73.1 (1), 70.5 (1), 63.3 (2), 51.5 (0), 45.4 (2), 39.2 (0), 29.7 (2), 27.5 (3, 3C), 27.1 (2), 19.5 (3), 19.4 (3).

LRMS *m/z* (CI, NH_3) 394 [$(M+NH_4)^+$, 100%].

HRMS (CI) Found: $(M+H)^+$, 376.1652. $C_{18}H_{30}ClO_6$ requires *M*, 376.1653.

Microanalysis: Anal. Calcd for $C_{18}H_{29}ClO_6$: C, 57.37; H, 7.70; Cl, 9.43. Found: C, 57.37; H, 7.64; Cl, 9.46.

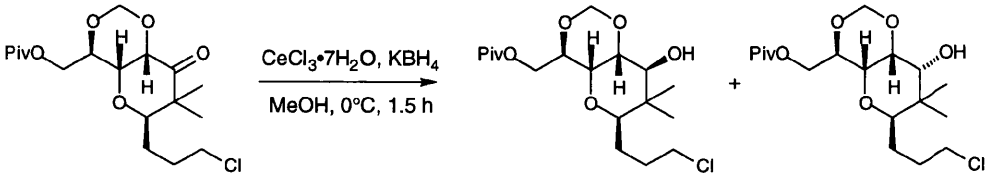


6.11b
$C_{18}H_{31}ClO_6$
Mol. Wt.: 378.87

6.10
$C_{18}H_{29}ClO_6$
Mol. Wt.: 376.87

Dess-Martin periodinane (2.7 g) was added in one portion to a stirred solution of alcohol **6.11b** (1.6 g, 4.3 mmol) in CH_2Cl_2 (20 mL). The reaction mixture was stirred at room temperature for 25 min and treated with saturated aqueous $Na_2S_2O_3$ (25 mL) and saturated aqueous $NaHCO_3$ (20 mL). After 1 h the phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was purified by flash column chromatography (SiO_2 10 g, hexanes:Et_2O 10-30%) to give ketone **6.10** (1.61 g, 4.3 mmol, 100%).

(1*R*,5*R*,6*R*,8*R*,10*S*)-5-(*tert*-Butylcarbonyloxy)methyl-8-(3-chloropropyl)-9,9-dimethyl-2,4,7-trioxabicyclo[4,4,0]decan-10-ol 6.11a and (1*R*,5*R*,6*R*,8*R*,10*R*)-5-(*tert*-Butylcarbonyloxy)methyl-8-(3-chloropropyl)-9,9-dimethyl-2,4,7-trioxabicyclo[4,4,0]decan-10-ol 6.11b.



6.10
$C_{18}H_{29}ClO_6$
Mol. Wt.: 376.87

6.11a
$C_{18}H_{31}ClO_6$
Mol. Wt.: 378.87

6.11b
$C_{18}H_{31}ClO_6$
Mol. Wt.: 378.87

A solution of ketone (1.80 g, 4.8 mmol) and cerium trichloride heptahydrate (2.6 g, 7.1 mmol) in anhydrous methanol (90 mL) were stirred at room temperature for 15 min and then cooled to 0°C. Solid KBH_4 (740 mg, 14.1 mmol) was added (gas evolution!). After 1.5 h acetone (1 mL) was added to the reaction mixture followed by saturated aqueous $NaHCO_3$ (50 mL). The methanol was removed *in vacuo* and the aqueous phase extracted with CH_2Cl_2 (3 x 50 mL). The combined organic extracts were washed with brine (50 mL), dried (Na_2SO_4) and concentrated. ^1H NMR spectrum of crude product showed a 1:2 ratio of diastereoisomers by integration of signals derived from C14-Me group [^1H NMR (360 MHz, $CDCl_3$): δ = 1.14 ppm (major) and 1.05 ppm (minor)]. The undesired alcohol **6.11b** was the major product. The crude product was purified by column chromatography (SiO_2 50 g, hexanes:Et_2O 30-50%) to give a mixture of alcohols **6.11a,b** (1.72 g, 4.56 mmol, 95%) as a colourless oil. The diastereoisomers were separated by column chromatography (SiO_2 150 g, hexanes:Et_2O 20-40%).

Analytical data for **6.11a**:

$[\alpha]_D^{20}$ +87.0 (*c* 2.0, $CHCl_3$).

ν_{max} film/cm^{-1} 3486 (br), 1740 (s), 1728 (s).

^1H NMR (400 MHz, $CDCl_3$): δ = 4.94 (1H, d, *J* = 6.4 Hz, OCH_AH_BO), 4.80 (1H, d, *J* = 6.8 Hz, OCH_AH_BO), 4.49 (1H, dd, *J* = 12.0, 2.0 Hz, C9-H_AH_B), 4.16 (1H, ddd, *J* = 10.4, 6.8, 1.6 Hz, C10-H), 4.06 (1H, dd, *J* = 10.4, 6.4 Hz), 4.03-3.94 (3H, m), 3.65-3.50 (2H, m, C18-H_2), 3.26 (1H, dd, *J* = 10.4, 1.6 Hz, C15-H), 2.24 (1H, br, OH), 2.10-1.90 (1H, m), 1.80-1.60 (2H, m), 1.50-1.37 (1H, m), 1.23 (9H, s, ^{t}BuCOO), 1.04 (3H, s, C14-Me), 0.93 (3H, s, C14-Me).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.6 (0), 86.7 (2), 78.1 (1), 72.8 (1), 71.4 (1), 69.4 (1), 67.4 (1), 63.8 (2), 45.4 (2), 40.8 (0), 39.0 (0), 29.7 (2), 27.3 (3, 3C), 26.3 (2), 23.1 (3), 12.6 (3).

LRMS *m/z* (CI) 379 [$(M+H)^+$, 100%].

Microanalysis: Anal. Calcd for $C_{18}H_{31}ClO_6$: C, 57.07; H, 8.19. Found: C, 57.11; H, 8.10.

Analytical data for **6.11b**:

$[\alpha]_D^{22}$ +66.3 (*c* 0.3, $CHCl_3$).

ν_{max} film/cm^{-1} 3496 (s), 1734 (s).

^1H NMR (360 MHz, $CDCl_3$): δ = 5.15 (1H, d, *J* = 5.8 Hz, OCH_AH_BO), 4.89 (1H, d, *J* = 5.8 Hz, OCH_AH_BO), 4.30 (2H, d, *J* = 5.7 Hz, C9-H_2), 4.21 (1H, dt, *J* = 10.4, 5.2 Hz, C10-H), 4.06 (1H, t, *J* = 3.8 Hz), 3.75-3.62 (3H, m), 3.59 (2H, t, *J* = 5.5 Hz, C18-H_2), 2.32 (1H, d, *J* = 8.1 Hz, OH), 2.00-1.58 (4H, m), 1.21 (9H, s, ^tBuCOO), 1.13 (3H, s, C14-Me), 0.96 (3H, s, C14-Me).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.3 (0), 89.1 (2), 78.0 (1, broad signal), 74.3 (1, broad signal), 73.1 (1), 70.2 (1), 65.4 (1), 62.3 (2), 45.1 (2), 38.9 (0), 38.5 (0), 29.3 (2), 27.2 (3, 3C), 24.0 (2), 22.6 (3), 22.2 (3, broad signal).

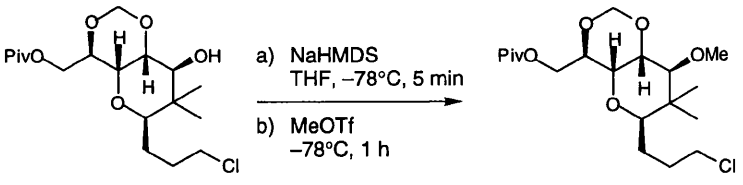
LRMS *m/z* (CI) 379 [$(M+H)^+$, 100%].

Microanalysis: Anal. Calcd for $C_{18}H_{31}ClO_6$: C, 57.07; H, 8.19. Found: C, 57.05; H, 8.05.

The following additional experiments were performed on a small scale (ca 5-7 mg) using a large excess of reagents.

$NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, –78°C	α/β = 2.3:1
$NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, 0°C	α/β = 2.5:1
$NaBH_4$, MeOH, –78°C	α/β = 3.5:1
$Na(CN)BH_3$, MeOH, 0°C→rt	α>β (slow reaction)
BH_3•THF complex, THF, –78°C→0°C	α only
l-Selectride, THF, –78°C→–50°C	α only
$NaBH_4$, $ZnCl_2$, MeOH, –85°C→10°C	α/β = 3:1
$LiAlH_4$, THF, –20°C	α>β
KBH_4 (35 mg), $CeCl_3 \cdot 7H_2O$ (30 mg), MeOH (1 mL) , –90°C→–20°C	α/β = 1:1

(1*R*,5*R*,6*R*,8*R*,10*S*)-5-(*tert*-Butylcarbonyloxy)methyl-8-(3-chloropropyl)-10-methoxy-9,9-dimethyl-2,4,7-trioxabicyclo[4,4,0]decan 6.12.



6.11a
$C_{18}H_{31}ClO_6$
Mol. Wt.: 378.87

6.12
$C_{19}H_{33}ClO_6$
Mol. Wt.: 392.91

A solution of alcohol **6.11a** (1.20 g, 3.16 mmol) in THF (4 + 2 + 1 mL) was added dropwise to a stirred solution of sodium bis(trimethylsilyl)amide (2.0 M in PhMe, 2.1 mL, 4.1 mmol) in THF (5 mL) at -78°C. After 5 min methyl trifluoromethanesulphonate (0.72 mL, 6.32 mmol) was added. The reaction mixture was stirred at -78°C for 1 h, treated with saturated aqueous $NaHCO_3$ (40 mL) and extracted with Et_2O (3 x 30 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography (SiO_2 20 g, hexanes:Et_2O 10-30%) to give methyl ether **6.12** (1.14 g, 2.90 mmol, 92%) as a colourless oil: $[\alpha]_D^{21}$ +54.7 (*c* 1.1, $CHCl_3$).

ν_{max} film/cm^{-1} 1732 (s), 1162 (s), 1112 (s), 1040(s).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.95 (1H, d, *J* = 6.8 Hz, OCH_AH_BO), 4.80 (1H, d, *J* = 6.8 Hz, OCH_AH_BO), 4.44 (1H, dd, *J* = 12.0, 2.0 Hz, C9-H_AH_B), 4.21-4.10 (1H, m, C10-H), 4.11 (1H, dd, *J* = 10.4, 6.8 Hz, C12-H), 3.97 (1H, dd, *J* = 12.0, 7.2 Hz, C9-H_AH_B), 3.90 (1H, dd, *J* = 10.8, 6.8 Hz, C11-H), 3.60-3.46 (2H, m, C18-H_2), 3.52 (3H, s, OMe), 3.49 (1H, d, *J* = 10.4 Hz, C13-H), 3.22 (1H, dd, *J* = 10.4, 1.4 Hz, C15-H), 2.03-1.87 (1H, m), 1.78-1.55 (2H, m), 1.38 (1H, ddt, *J* = 14.8, 10.2, 5.0 Hz), 1.19 (9H, s, ^{t}BuCOO), 0.97 (3H, s, C14-Me), 0.83 (3H, s, C14-Me).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.4 (0), 87.0 (2), 79.3 (1), 78.1 (1), 73.5 (1), 71.3 (1), 67.4 (1), 63.8 (2), 61.7 (3), 45.3 (2), 41.7 (0), 38.9 (0), 29.6 (2), 27.2 (3, 3C), 26.2 (2), 23.2 (3), 13.5 (3).

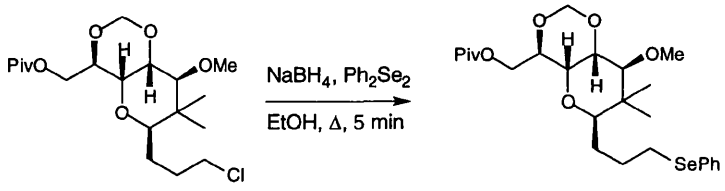
LRMS *m/z* (CI) 393 [$(M+H)^+$, 100%].

HRMS (CI) Found: $(M+H)^+$, 393.2040. $C_{19}H_{34}ClO_6$ requires *M*, 393.2044.

Microanalysis: Anal. Calcd for $C_{19}H_{33}ClO_6$: C, 58.09; H, 8.41. Found: C, 58.19; H, 8.41

(1*R*,5*R*,6*R*,8*R*,10*S*)-5-(*tert*-Butylcarbonyloxy)methyl-10-methoxy-9,9-dimethyl-8-(3-phenylselenylpropyl)-2,4,7-trioxabicyclo[4,4,0]decan 6.13.

Substitution of a halide with sodium phenylselenide is described in the literature[119].



6.12
$C_{19}H_{33}ClO_6$
Mol. Wt.: 392.91

6.13
$C_{25}H_{38}O_6Se$
Mol. Wt.: 513.53

Sodium borohydride (165 mg, 4.34 mmol) was added in several batches to a stirred suspension of diphenyl diselenide (680 mg, 2.17 mmol) in anhydrous ethanol (8 mL) to cause exothermic reaction. A solution of chloride **6.12** (1.12 g, 2.85 mmol) in THF (2 + 2 mL) was then added *via* cannula and the resulting mixture was heated at reflux for 5 min. The reaction mixture was then cooled to room temperature, poured onto saturated aqueous $NaHCO_3$ (60 mL) and extracted with Et_2O (3 x 50 mL). The combined organic extracts were washed with 2M $NaOH_{(aq)}$ (40 mL), brine (40 mL) dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography (SiO_2 20 g, hexanes:Et_2O 0-40%) to give selenide **6.13** (1.43 g, 2.79 mmol, 98%) as a colourless oil: $[\alpha]_D^{20}$ +71.3 (*c* 1.6, $CHCl_3$).

ν_{max} film/cm^{-1} 1732 (s), 1580 (m), 1186 (s), 1162 (s),1112 (s), 1040 (s).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.47 (1H, dd, J = 8.0, 2.4 Hz), 7.50-7.40 (1H, m), 7.30-7.18 (3H, m), 4.95 (1H, d, J = 6.4 Hz, OCH_AH_BO), 4.81 (1H, d, J = 6.4 Hz, OCH_AH_BO), 4.42 (1H, dd, J = 12.0, 2.0 Hz, C9-H_AH_B), 4.18-4.08 (1H, m, C10-H), 4.13 (1H, dd, J = 10.0, 6.8 Hz, C12-H), 3.98 (1H, dd, J = 12.4, 7.2 Hz, C9-H_AH_B), 3.91 (1H, dd, J = 10.4, 6.8 Hz, C11-H), 3.53 (3H, s, OMe), 3.37 (1H, d, J = 10.0 Hz, C13-H), 3.21 (1H, dd, J = 10.0, 1.2 Hz, C15-H), 2.90 (2H, t, J = 7.2 Hz, C18-H_2), 2.00-1.85 (1H, m), 1.75-1.50 (2H, m), 1.38 (1H, ddt, J = 14.7, 10.0, 4.8 Hz), 1.21 (9H, s, ^{t}BuCOO), 0.95 (3H, s, C14-Me), 0.83 (3H, s, C14-Me).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.3 (0), 132.8 (1, 2C), 130.4 (0), 129.0 (1, 2C), 126.8 (1), 86.9 (2), 79.3 (1), 78.2 (1), 73.4 (1), 71.3 (1), 67.3 (1), 63.7 (2), 61.7 (3), 41.6 (0), 38.9 (0), 28.7 (2), 28.0 (2), 27.2 (3, 3C; 2, 1C), 23.2 (3), 13.5 (3).

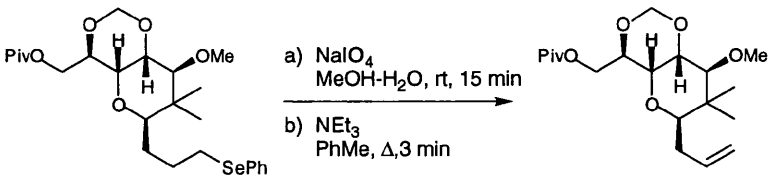
LRMS *m/z* (EI) 514 [(M+H)$^+$, 33%], 357 (15), 243 (15), 193 (20), 113 (25), 71 (100).

HRMS (EI) Found: (M+H)$^+$, 514.1830. $C_{25}H_{38}O_6Se$ requires *M*, 514.1835.

Microanalysis: Anal. Calcd for $C_{25}H_{38}O_6Se$: C, 58.48; H, 7.41. Found: C, 58.47; H, 7.48.

(1*R*,5*R*,6*R*,8*R*,10*S*)-5-(*tert*-Butylcarbonyloxy)methyl-10-methoxy-9,9-dimethyl-8-(prop-2-enyl)-2,4,7-trioxabicyclo[4,4,0]decan 6.14.

Oxidation of a selenide to a selenoxide and elimination of a selenoxide are described in the literature[13, 14].



6.13
$C_{25}H_{38}O_6Se$
Mol. Wt.: 513.53

6.14
$C_{19}H_{32}O_6$
Mol. Wt.: 356.45

Sodium metaperiodate (970 mg, 4.52 mmol) was added in one portion to a stirred mixture of selenide **6.13** (1.40 g, 2.73 mmol), water (16 mL) and MeOH (40 mL) at room temperature. The reaction mixture was stirred for 15 min then diluted with water (50 mL) and extracted with CH_2Cl_2 (5 x 50 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was treated with toluene (10 mL) and triethylamine (10 mL) and heated at reflux for 3 min using a heat gun. The yellow reaction mixture was cooled to room temperature, poured onto saturated aqueous $NaHCO_3$ (50 mL) and extracted with CH_2Cl_2 (3 x 30 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated at room temperature. The residue was purified by column chromatography (SiO_2 20 g, hexanes:Et_2O 0-30%) to give olefin **6.14** (940 mg, 2.64 mmol, 97%) as a colourless oil: $[\alpha]_D^{22}$ +25.9 (*c* 1.4, $CHCl_3$).

ν_{max} film/cm^{-1} 1732 (s), 1480 (m), 1284 (s).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.84 (1H, ddt, *J* = 18.0, 9.6, 6.8 Hz, C17-H), 5.07 (1H, ddm, *J* = 5.6, 1.2 Hz, C18-H_AH_B), 5.04 (1H, dm, *J* = 1.2 Hz, C18-H_AH_B), 4.99 (1H, d, *J* = 6.4 Hz, OCH_AH_BO), 4.86 (1H, d, *J* = 6.8 Hz, OCH_AH_BO), 4.47 (1H, dd, *J* = 12.4, 2.0 Hz, C9-H_AH_B), 4.20-4.15 (1H, m, C10-H), 4.18 (1H, dd, *J* = 10.4, 6.8 Hz, C12-H), 4.06 (1H, dd, *J* = 12.0, 6.4 Hz, C9-H_AH_B), 3.99 (1H, dd, *J* = 10.8, 6.8 Hz, C11-H), 3.57 (3H, s, OMe), 3.44 (1H, d, *J* = 10.4 Hz, C13-H), 3.30 (1H, dd, *J* = 10.0, 2.4 Hz, C15-H), 2.20 (1H, dddt, *J* = 14.4, 6.8, 2.2, 1.2 Hz, C16-H_AH_B), 2.07 (1H, dddt, *J* = 14.4, 10.2, 7.1, 1.2 Hz, C16-H_AH_B), 1.24 (9H, s, ^{t}BuCOO), 1.02 (3H, s, C14-Me), 0.90 (3H, s, C14-Me).

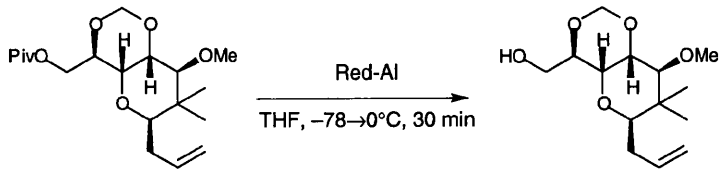
^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.5 (0), 136.0 (1), 116.8 (2), 87.2 (2), 79.5 (1), 78.7 (1), 73.6 (1), 71.4 (1), 67.5 (1), 63.6 (2), 61.8 (3), 41.7 (0), 39.0 (0), 33.5 (2), 27.3 (3, 3C), 23.3 (3), 13.6 (3).

LRMS *m/z* (CI) 357 [$(M+H)^+$, 100%].

HRMS (CI) Found: $(M+H)^+$, 357.2277. $C_{19}H_{33}O_6$ requires *M*, 357.2276.

Microanalysis: Anal. Calcd for $C_{19}H_{32}O_6$: C, 64.04; H, 9.00. Found: C, 64.04; H, 9.19.

(1*R*,5*R*,6*R*,8*R*,10*S*)-5-hydroxymethyl-10-methoxy-9,9-dimethyl-8-(prop-2-enyl)-2,4,7-trioxabicyclo[4,4,0]decan 6.15.



6.14
$C_{19}H_{32}O_6$
Mol. Wt.: 356.45

6.15
$C_{14}H_{24}O_5$
Mol. Wt.: 272.34

To a solution of ester **6.14** (814 mg, 2.29 mmol) in THF (10 mL) at –70°C was added Red-Al (1.55 M in PhMe and THF, 3 mL, 4.65 mmol) in a dropwise fashion over 5 min. The cool bath was removed and the clear colourless reaction mixture was allowed to warm up to 0°C over 30 min. After such time acetone (0.4 mL) was added. The mixture was then poured onto ice cold 2M $NaOH_{(aq)}$ (10 mL) and CH_2Cl_2 (20 mL) and H_2O (20 mL) were added. The clear colourless phases were then separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated. Purification by column chromatography (SiO_2 40 g, hexanes/Et_2O 50-60%) afforded the alcohol **6.15** (608 mg, 2.24 mmol, 98%) as a clear colourless oil: $[\alpha]_D^{23}$ +102.3 (*c* 1.2, $CHCl_3$).

ν_{max} film/cm^{-1} 3465 (br), 1640 (m), 1468 (s), 1177 (s), 1110 (s).

^1H NMR assignments made using 2D H-H correlation spectra.

^1H NMR (400 MHz, $CDCl_3$): δ = 5.77 (1H, ddt, *J* = 17.0, 10.4, 6.8 Hz, C17-H), 5.07 (1H, dm, *J* = 5.2 Hz, C18-H_AH_B), 5.04-5.01 (1H, m, C18-H_AH_B), 5.01 (1H, d, *J* = 6.4 Hz, OCH_AH_BO), 4.82 (1H, d, *J* = 6.4 Hz, OCH_AH_BO), 4.15 (1H, dd, *J* = 10.4, 6.4 Hz, C12-H), 4.05-3.96 (2H, m, C11-H, C10-H), 3.83 (1H, ddd, *J* = 12.0, 6.8, 2.8 Hz collapses to dd, *J* = 12.0, 2.8 Hz after D_2O shake, CH_AH_BOH), 3.66 (1H, ddm, *J* = 11.6, 5.6 Hz collapses to dd, *J* = 11.6, 5.2 Hz after D_2O shake, CH_AH_BOH), 3.56 (3H, s, OMe), 3.43 (1H, d, *J* = 10.4 Hz, C13-H), 3.26 (1H, dd, *J* = 10.4, 2.0 Hz, C15-H), 2.27 (1H, t, *J* = 6.4 Hz, OH), 2.16 (1H, dddt, *J* = 11.3, 7.4, 2.0, 1.2 Hz, C16-H_AH_B), 2.03 (1H, dddt, *J* = 14.2, 10.3, 6.8, 0.8 Hz, C16-H_AH_B), 1.00 (3H, s, C14-Me), 0.87 (3H, s, C14-Me).

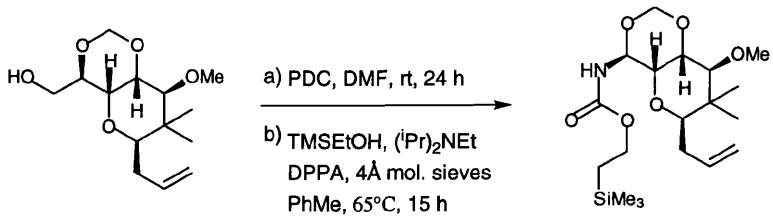
^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.9 (1), 117.0 (2), 87.0 (2), 79.3 (1), 78.5 (1), 73.5 (1), 73.2 (1), 68.0 (1), 63.0 (2), 61.9 (3), 41.7 (0), 33.5 (2), 23.2 (3), 13.2 (3).

LRMS *m/z* (CI) 373 [$(M+H)^+$, 50%], 231 (100).

HRMS (CI) Found: $(M+H)^+$, 273.1704. $C_{14}H_{25}O_5$ requires *M*, 273.1702.

(1*R*,5*R*,6*R*,8*R*,10*S*)-9,9-dimethyl-10-methoxy-8-(prop-2-enyl)-5-{*N*-[(2-trimethylsilyl)ethoxycarbonyl]amino}-2,4,7-trioxabicyclo[4,4,0]decan 6.17.

Curtius rearrangement performed using the conditions of Shioiri.[53]



6.15
$C_{14}H_{24}O_5$
Mol. Wt.: 272.34

6.17
$C_{19}H_{35}NO_6Si$
Mol. Wt.: 401.57

Pyridinium dichromate (3.0 g, 7.97 mmol) was added to a mixture of alcohol **6.15** (200 mg, 0.735 mmol) in anhydrous DMF (4 mL) and stirred at room temperature. After 8 h a further portion of pyridinium dichromate (1.0 g, 2.66 mmol) was added and the mixture stirred for a further 15 h. After such time H_2O (60 mL) was added and the mixture extracted with EtOAc (5 x 25 mL). The combined organic extracts were washed with brine (20 mL), dried (Na_2SO_4) and concentrated. The residue was taken up in toluene (2 x 5 mL) and concentrated twice to give crude acid **6.16** (290 mg) as a brown oil.

The crude acid **6.16** was dissolved in anhydrous toluene (2 mL) to which freshly activated 4Å molecular sieves (8) and anhydrous *N*-ethyldiisopropylamine (0.2 mL, 148 mg, 1.15 mmol) were added. 2-Trimethylsilylethanol (0.8 mL, 660 mg, 5.58 mmol), dried by the addition of freshly activated 4Å molecular sieves (8), and diphenyl phosphoryl azide (0.2 mL, 255 mg, 0.93 mmol) were then added at concomitantly. The mixture was plunged into an oil bath at 65°C and evolution of N_2 gas was observed over a period of 8 min. After heating at 65°C for 1 h the green reaction mixture was quenched by the addition of saturated aqueous $NaHCO_3$ (18 mL) and extracted with CH_2Cl_2 (3 x 25 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography (SiO_2 15 g, hexanes:Et_2O 10-25%) to give carbamate **6.17** (171 mg, 4.26 mmol, 58%) as a pale yellow oil: $[\alpha]_D^{23}$ +46.7 (*c* 0.09, $CHCl_3$).

ν_{max} film/cm^{-1} 1720 (s), 1542 (m), 1109 (s), 1032 (s).

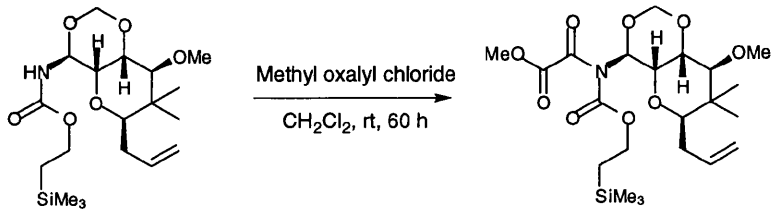
^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.72 (1H, ddt, *J* = 16.8, 10.0, 6.8 Hz, C17-H), 5.53 (1H, t, *J* = 9.2 Hz, C10-H), 5.30 (1h, d, *J* = 9.2 Hz, NH), 5.14 (1H, d, *J* = 7.2 Hz, OCH_AH_BO), 5.03 (1H, dq, *J* = 17.2, 1.6 Hz, C18-H_AH_B), 4.95 (1H, dm, *J* = 7.2 Hz, C18-H_AH_B), 4.86 (1H, d, *J* = 7.2 Hz, OCH_AH_BO), 4.25-4.18 (3H, m, $OCH_2CH_2SiMe_3$ and C11-H), 3.80 (1H, dd, *J* = 10.0, 6.8 Hz, C12-H), 3.57 (3H, s, OMe), 3.45 (1H, d, *J* = 10.4 Hz, C13-H), 3.31 (1H, d, *J* = 9.2 Hz, C15-H), 2.18 (1H, ddm, *J* = 6.8, 2.0 Hz, C16-H_AH_B), 2.10-2.00 (1H, m, C16-H_AH_B), 1.05-0.98 (2H, m, CH_2SiMe_3), 1.01 (3H, s, C14-Me), 0.88 (3H, s, C14-Me), 0.05 (9H, s, $SiMe_3$).

^{13}C NMR (90 MHz, $CDCl_3$): δ = 156.1 (0), 135.9 (1), 116.3 (2), 86.7 (2), 79.6 (1), 78.6 (1), 76.5 (1), 74.9 (1), 70.8 (1), 64.1 (2), 62.0 (3), 41.9 (0), 33.6 (2), 23.3 (3), 17.8 (2), 13.5 (3), –1.3 (3, 3C).

LRMS *m/z* (CI) 402 [$(M+H)^+$, 70%], 374 (100).

HRMS (CI) Found: $(M+H)^+$, 402.2315. $C_{19}H_{36}O_6NSi$ requires *M*, 402.2312.

(1*R*,5*R*,6*R*,8*R*,10*S*)-9,9-dimethyl-10-methoxy-5-{*N*-(methyloxalyl)-*N*-[(2-trimethylsilyl)ethoxycarconyl]amino}-8-(prop-2-enyl)-2,4,7-trioxabicyclo[4,4,0]decan 6.18.



6.17
$C_{19}H_{35}NO_6Si$
Mol. Wt.: 401.57

6.18
$C_{22}H_{37}NO_9Si$
Mol. Wt.: 487.62

To a solution of carbamate **6.17** (68 mg, 0.17 mmol) in CH_2Cl_2 was added DMAP (124 mg, 1.0 mmol, recrystallised from CH_2Cl_2:Et_2O:hexanes) and methyl oxalyl chloride (90μL, 0.98 mmol). The mixture was stirred for 91 h and concentrated. The residue was purified by column chromatography (SiO_2 6 g, hexanes:EtOAc 19:1) to give ester **6.18** (55 mg, 0.11 mmol, 66%) as a clear colourless oil and starting carbamate **6.17** (6 mg, 0.15 mmol, 9%) as a clear colourless oil.

$[\alpha]_D^{22}$ +63.8 (*c* 0.8, $CHCl_3$).

ν_{max} film/cm^{-1} 1776 (m), 1689 (s), 1644 (s), 1470 (s).

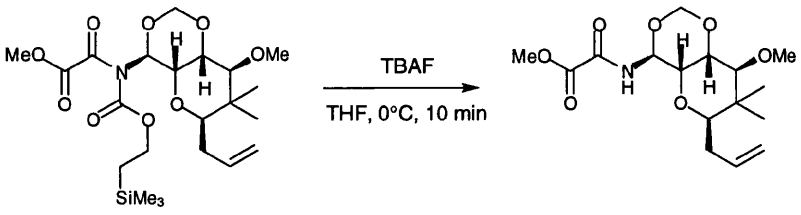
^1H NMR (360 MHz, $CDCl_3$): δ = 6.13 (1H, d, *J* = 10.5 Hz, C10-H), 5.68 (1H, ddt, *J* = 17.0, 10.1, 6.8 Hz, C17-H), 5.11 (1H, d, *J* = 6.7 Hz, OCH_AH_BO), 5.02-4.93 (2H, m, C18-H_2), 4.98 (1H, d, *J* = 6.8 Hz, OCH_AH_BO), 4.86 (1H, dd, *J* = 10.4, 7.3 Hz, C11-H), 4.35 (2H, ddd, *J* = 8.5, 6.3, 3.7 Hz, $OCH_2CH_2SiMe_3$), 4.33 (1H, dd, *J* = 10.5, 7.3 Hz, C12-H), 3.90 (3H, s, C(O)OMe), 3.59 (3H, s, OMe), 3.47 (1H, d, *J* = 10.5 Hz, C13-H), 3.29 (1H, dd, *J* = 9.9, 2.1 Hz, C15-H), 2.15 (1H, dddt, *J* = 13.0, 7.2, 2.2, 1.5 Hz, C16-H_AH_B), 2.03 (1H, dddt, *J* = 14.4, 10.0, 6.9, 1.2 Hz, C16-H_AH_B), 1.12 (2H, ddd, *J* = 8.4, 6.2, 3.7, CH_2SiMe_3), 1.02 (3H, s, C14-Me), 0.88 (3H, s, C14-Me), 0.07 (9H, s, $SiMe_3$).

^{13}C NMR (90 MHz, $CDCl_3$): δ = 162.9 (0), 161.3 (0), 152.5 (0), 135.7 (1), 116.6 (2), 87.8 (2), 79.5 (1), 78.9 (1), 77.2 (1), 75.2 (1), 67.7 (2), 67.0 (1), 62.0 (3), 53.1 (3), 41.8 (0), 33.7 (2), 23.1 (3), 17.5 (2), 13.3 (3), –1.5 (3, 3C).

LRMS *m/z* (EI) 487 [$M^{+\bullet}$, 1%], 446 (7), 449 (8), 374 (14), 362 (35).

HRMS (EI) Found: $M^{+\bullet}$, 487.2219. $C_{22}H_{37}O_9NSi$ requires *M*, 487.2238.

(1*R*,5*R*,6*R*,8*R*,10*S*)-9,9-Dimethyl-10-methoxy-5-[*N*-(methyloxalyl)amino]-8-(prop-2-enyl)-2,4,7-trioxabicyclo[4,4,0]decan 6.19.



6.18
$C_{22}H_{37}NO_9Si$
Mol. Wt.: 487.62

6.19
$C_{16}H_{25}NO_7$
Mol. Wt.: 343.37

TBAF (~95%, 400 mg, 1.45 mmol) was added to a solution of carbamate **6.18** (155 mg, 0.318 mmol) in THF (6 mL) at 0°C. After 2 min the mixture was diluted with CH_2Cl_2 (40 mL) and washed with H_2O (60 mL). The aqueous phase was extracted with CH_2Cl_2 (2 x 20 mL) and the combined organic extracts dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography (SiO_2 15 g, hexanes:Et_2O 50%) to give the desired amide **6.19** (90 mg, 0.262 mmol, 83%) as a white solid: mp 169-170°C (hexanes:Et_2O).

$[\alpha]_D^{23}$ +76.2 (*c* 0.6, $CHCl_3$).

ν_{max} KBr/cm^{-1} 1737 (m), 1701 (s), 1036 (s).

^{1}H NMR (360 MHz, $CDCl_3$): δ = 7.53 (1H, d, *J* = 9.2 Hz, NH), 5.73 (1H, t, *J* = 9.7 Hz, C10-H), 5.62 (1H, ddt, *J* = 17.0, 10.1, 6.9 Hz, C17-H), 5.15 (1H, d, *J* = 7.0 Hz, OCH_AH_BO), 4.97 (1H, dm, *J* = 17.1 Hz, C18-H_AH_B), 4.91-4.85 (1H, m, C18-H_AH_B), 4.88 (1H, d, *J* = 7.3 Hz, OCH_AH_BO), 4.25 (1H, dd, *J* = 10.3, 6.8 Hz, C12-H), 3.93 (3H, s, $C(O)OCH_3$), 3.90 (1H, dd, *J* = 9.8, 6.8, C11-H), 3.57 (3H, s, OMe), 3.45 (1H, d, *J* = 10.3 Hz, C13-H), 3.28 (1H, dd, *J* = 9.9, 1.4 Hz, C15-H), 2.16 (1H, ddm, *J* = 14.0, 5.5 Hz, C16-H_AH_B), 2.0 (1H, ddd *J* = 17.0, 5.6, 5.5 Hz, C16-H_AH_B), 1.01 (3H, s, C14-Me), 0.88 (3H, s, C14-Me).

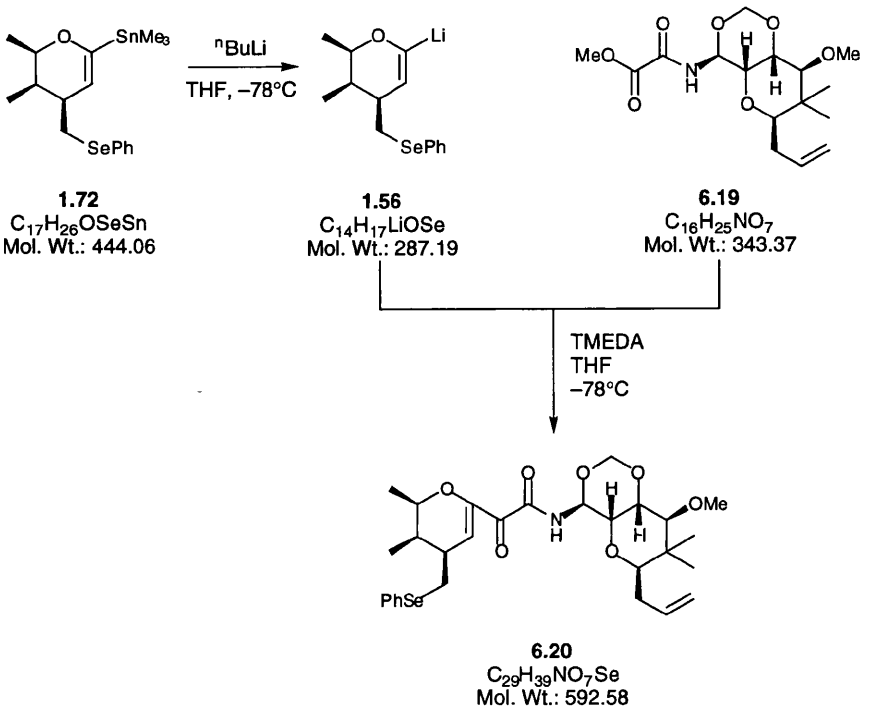
^{13}C NMR (90 MHz, $CDCl_3$): δ = 160.3 (0), 156.5 (0), 135.7 (1), 116.5 (2), 86.9 (2), 79.5 (1), 78.9 (1), 74.8 (1), 74.3 (1), 70.6 (1), 62.0 (3), 54.0 (3), 41.9 (0), 33.4 (2), 23.2 (3), 13.6 (3).

LRMS *m/z* (CI) 344 [$(M+H)^+$, 100%].

HRMS (CI) Found: $(M+H)^+$, 344.1708. $C_{16}H_{26}O_7N$ requires *M*, 344.1709.

Microanalysis: Anal. Calcd for $C_{16}H_{25}NO_7$: C, 55.98; H, 7.29; N, 4.08. Found: C, 56.08; H, 7.14; N, 4.04.

(1*R*,5*S*,6*S*,8*S*,10*S*)-5{[(2*R*,3*R*,4*S*)-3,4-dihydro-2,3-dimethyl-4-phenylselenylmethyl-2*H*-pyran-6-yl]-oxoethanamido}-9,9-dimethyl-10-methoxy-8-[prop-2-enyl]-2,4,7-trioxabicyclo[4.4.0]decane 6.20



A flame dried 25 mL Schlenk flask was charged with stananne **1.72** (230 mg, 0.52 mmol) in THF (3 mL) and cooled to –78°C. ^{n}BuLi (0.61 M in hexanes, 0.84 mL, 0.52 mmol) was added dropwise over 10 min keeping the reaction mixture at –78°C. After 15 min TMEDA (0.35 mL, 0.44 g, 3.80 mmol) was added dropwise to the yellow solution over 1 min. The mixture was stirred for a further 15 min at –78°C before a cold solution of ester **6.19** (60 mg, 0.174 mmol) in THF (2 + 2 mL) was added *via* cannula. The clear colourless reaction mixture was stirred for 2 h at –78°C before being quenched by the addition of saturated aqueous NH_4Cl (6 mL) and stirred vigorously for 15 min. The mixture was then extracted with CH_2Cl_2 (3 x 20 mL) and the combined organic extracts dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography (SiO_2 7 x 2.5 cm, hexanes:Et_2O 10-40%) to give the desired product **6.20** (80 mg, 0.135 mmol, 78%) as a white solid. Recrystallisation from hexanes:Et_2O gave clear colourless rock crystals for analysis which were analysed by X-ray crystallography to confirm the absolute stereochemistry of **6.20** (see appendix A).

mp 144-145°C (hexanes:Et_2O)

$[\alpha]_D^{21}$ –32.0 (*c* 0.5, $CHCl_3$).

ν_{max} KBr/cm^{-1} 1670 (s), 1124 (s), 1024 (s).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.56-7.48 (3H, m), 7.31-7.25 (3H, m), 7.09 (1H, dd, *J* = 2.0, 1.6 Hz, C5-H), 5.72 (1H, t, *J* = 9.6 Hz), 5.62 (1H, ddt, *J* = 17.0, 10.2, 6.8 Hz, C17-H), 5.16 (1H, d, *J* = 6.9 Hz, OCH_AH_BO),

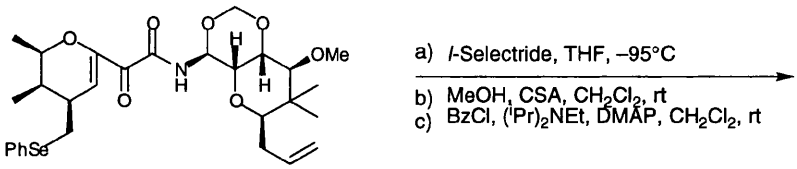
5.55 (1H, ddm, J = 17.2, 2.0 Hz, C18-H_AH_B), 4.90 (1H, d, J = 6.9 Hz, OCH_AH_BO), 4.84 (1H, ddm, J = 10.2, 1.6 Hz, C18-H_AH_B), 4.25 (1H, dd, J = 10.3, 6.7 Hz, C12-H),4.10 (1H, dq, J = 1.2, 6.4 Hz, C2-H), 3.92 (1H, dd, J = 9.8, 6.7 Hz, C11-H), 3.58 (3H, s, C13-OMe), 3.46 (1H, d, J = 10.3 Hz, C13-H), 3.29 (1H, dd, J = 10,0, 2.0 Hz, C15-H), 2.98-2.93 (2H, m, CH_2SePh), 2.90-2.82 (1H, m, C4-H), 2.15 (1H, ddm, J = 13.6, 5.5 Hz, C16-H_AH_B), 2.08-1.98 (2H, m, C16-H_AH_B and C3-H), 1.39 (3H, d, J = 6.5 Hz, C2-Me), 1.03 (3H, s, C14-Me), 0.89 (3H, s, C14-Me), 0.82 (3H, s, d, J = 7.0 Hz, C3-Me).

^{13}C NMR (90 MHz, $CDCl_3$): δ = 179.7 (0), 160.7 (0), 148.7 (0), 135.8 (1), 133.4 (1, 2C), 129.4 (1, 2C), 129.3 (0), 127.6 (1), 124.8 (1), 116.6 (2), 86.9 (2), 79.6 (1), 78.9 (1), 76.8 (1), 74.8 (1), 74.0 (1), 70.4 (1), 62.0 (3), 41.8 (0), 39.1 (1), 33.4 (1, 2, 2C), 29.6 (2), 23.3 (3), 18.3 (3), 13.7 (3), 6.1 (3).

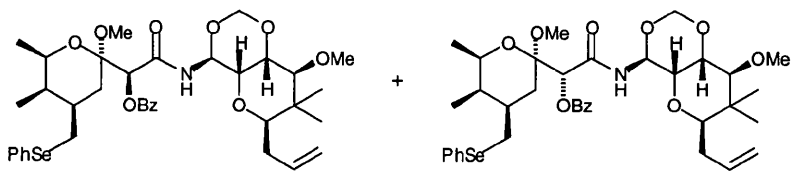
LRMS *m/z* (EI) 593 [$(M+H)^+$, 3%], 435 (10), 223 (50), 151 (52), 87 (100).

Microanalysis: Anal. Calcd for $C_{29}H_{39}NO_7Se$: C, 58.78; H, 6.59; N, 2.36. Found: C, 58.67; H, 6.58; N, 2.25.

(1*R*,5*S*,6*S*,8*S*,10*S*)-5{[(2*R*,3*R*,4*S*,6*S*)-2,3-Dimethyl-2,3-dimethyl-6-methoxy-4-phenylselenylmethyl-tetrahydro-2*H*-pyran-6-yl]-[(2*S*)-2-benzoylcarbonyloxyethanamido]}-9,9-dimethyl-10-methoxy-8-[prop-2-enyl]-2,4,7-trioxabicyclo[4.4.0]decane 6.21a and (1*R*,5*S*,6*S*,8*S*,10*S*)-5{[(2*R*,3*R*,4*S*,6*S*)-2,3-dimethyl-2,3-dimethyl-6-methoxy-4-phenylselenylmethyl-tetrahydro-2*H*-pyran-6-yl]-[(2*R*)-2-benzoylcarbonyloxyethanamido]}-9,9-dimethyl-10-methoxy-8-[prop-2-enyl]-2,4,7-trioxabicyclo[4.4.0]decane 6.21b



6.20
$C_{29}H_{39}NO_7Se$
Mol. Wt.: 592.58



6.21a
$C_{37}H_{49}NO_9Se$
Mol. Wt.: 730.75

6.21b
$C_{37}H_{49}NO_9Se$
Mol. Wt.: 730.75

l-Selectride (1 M in THF, 0.27 mL, 0.27 mmol) was added dropwise to a solution of ketone **6.20** (85 mg, 0.144 mmol) in THF (2.7 mL) at –95°C over 15 min. After stirring at –95°C for 15 min the reaction was quenched by the addition of brine (5 mL) and CH_2Cl_2 (5 mL). The mixture was stirred vigorously for a further 15 min and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated to give a clear colourless oil (102 mg).

The clear colourless oil (102 mg) was dissolved in CH_2Cl_2 (4.5 mL) and MeOH (0.4 mL) to which camphor sulphonic acid (4 mg) was added at room temperature. The mixture was stirred at room temperature for 40 min before K_2CO_3 (16 mg) was added. The mixture was then stirred for 30 min and poured onto saturated aqueous NaHCO3 (6 mL). The mixture was extracted with CH_2Cl_2 (3 x 20 mL) and the combined organic extracts were dried (Na_2SO_4) and concentrated to give a clear yellow oil (114 mg).

The clear yellow oil (114 mg) was dissolved in CH_2Cl_2 (4.5 mL) to which DMAP (34 mg, 0.29 mmol), *N*-ethyldiisopropylamine (0.25 mL, 186 mg, 1.44 mmol) and benzoyl chloride (47 μL, 0.41 mmol) were added at room temperature. The mixture was stirred at room temperature for 1 h before MeOH (0.4 mL) was added. After stirring for 10 min brine (6 mL) was added and the mixture extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated to give a yellow solid. Column chromatography (SiO_2 20 g, hexanes:Et_2O 1:1) afforded the desired benzoates **6.21a,b** (96 mg, 0.132 mmol, 91%) as a white solid. ^1H NMR spectroscopic analysis (C_6D_6, referenced to 7.16 ppm) of the mixture revealed doublets at $\delta = 4.53$ (major) and 4.71 (minor) attributed to the OCH_AH_BO proton corresponding to a favourable 5:1 mixture of diastereoisomeric benzoates. The diastereoisomers were separated by column chromatography (SiO_2 25 g, CH_2Cl_2:Et_2O 20:1) to give the desired diastereoisomer **6.21a** (66 mg, 0.090 mmol, 63%) as a white foam and the undesired diastereoisomer **6.21b** (10 mg, 0.0137 mmol, 10%) as a white foam and a mixture of diastereoisomers **6.21a,b** (20 mg, 0.027 mmol, 20%) as a white solid.

Analytical data for **6.21a**:

mp 72-76°C

$[\alpha]_D^{23}$ +103.8 (*c* 0.8, $CHCl_3$).

ν_{max} KBr/cm^{-1} 1732 (s), 1704 (s), 1272 (m), 1033 (s).

^1H NMR (360 MHz, C_6D_6 referenced to 7.16 ppm): $\delta = 8.32$ (2H, dd, $J = 8.2$, 1.6 Hz), 7.47 (2H, dd, $J = 7.8$, 1.5 Hz), 7.42 (1H, d, $J = 9.6$ Hz, NH), 7.10-6.92 (6H, m), 6.06 (1H, ddt, $J = 16.5$, 10.3, 6.9 Hz, C17-H), 5.95 (1H, s, C7-H), 5.94 (1H, t, $J = 9.8$ Hz, C10-H), 5.14 (1H, ddm, $J = 10.1$, 0.9 Hz, C18-H_AH_B), 5.06 (1H, ddm, $J = 17.1$, 1.2 Hz, C18-H_AH_B), 4.59 (1H, d, $J = 6.9$ Hz, OCH_AH_BO), 4.53 (1H, d, $J = 6.9$ Hz, OCH_AH_BO), 4.32 (1H, dd, $J = 10.3$, 6.8 Hz, C12-H), 3.79 (1H, dd, $J = 9.7$, 6.8 Hz, C11-H), 3.60-3.52 (2H, m, C15-H and C2-H), 3.27 (3H, s, OMe), 3.07 (1H, d, $J = 10.4$ Hz, C13-H), 2.89 (3H, s, OMe), 2.87-2.84 (1H, m, CH_AH_BSePh), 2.83 (1H, dd, $J = 14.4$, 11.9 Hz, CH_AH_BSePh), 2.49-2.38 (1H, m with 10 lines, C4-H), 2.29 (1H, dd, $J = 13.5$, 3.6 Hz, C5-H), 2.17-2.03 (1H, m, C16-H_AH_B), 2.03 (1H, dd, $J = 14.4$, 7.6 Hz, C16-H_AH_B), 1.86 (1H, t, $J = 13.0$ Hz, C5-H), 1.60-1.50 (1H, m, C3-H), 0.87 (3H, s, C14-Me), 0.85 (3H, d, $J = 6.7$ Hz, C2-Me), 0.80 (3H, d, $J = 6.8$ Hz, C3-Me), 0.79 (3H, s, C14-Me).

^{13}C NMR (90 MHz, C_6D_6 referenced to 128.4 ppm): δ = 166.7 (0), 166.0 (0), 137.7 (1), 133.6 (1), 133.2 (1, 2C), 131.4 (0), 130.8 (0), 130.7 (1, 2C), 129.7 (1, 2C), 129.0 (1, 2C), 127.3 (1), 116.3 (2), 99.8 (0), 87.1 (2), 79.4 (1), 78.9 (1), 75.7 (1), 74.9 (1), 72.9 (1), 72.5 (1), 71.0 (1), 61.7 (3), 48.3 (3), 42.0 (0), 35.9 (1), 35.5 (1), 34.4 (2), 32.5 (2), 31.6 (2), 23.5 (3), 18.5 (3), 14.1 (3), 5.0 (3).

LRMS *m/z* (EI) 731 [$M^{+\bullet}$, 0.4%].

HRMS (EI) Found: $M^{+\bullet}$, 731.2575. $C_{37}H_{49}NO_9Se$ requires *M*, 731.2576.

Analytical data for **6.21b**:

mp 74-79°C

$[\alpha]_D^{23}$ +17.5 (*c* 0.4, $CHCl_3$).

ν_{max} KBr/cm^{-1} 1733 (s), 1708 (s), 1264 (m), 1128 (s), 1107 (s), 1026 (s).

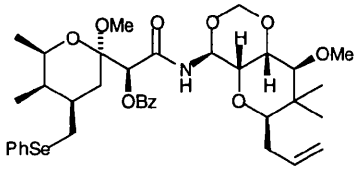
^1H NMR (360 MHz, C_6D_6 referenced to 7.16 ppm): δ= 8.32 (2H, dd, *J* = 8.2, 1.5 Hz), 7.49-7.38 (3H, m), 7.11-6.92 (6H, m), 6.19 (1H, ddt, *J* = 16.9, 10.2, 6.5 Hz, C17-H), 6.02 (1H, t, *J* = 9.8 Hz, C10-H), 5.92 (1H, s, C7-H), 5.55 (1H, dm, *J* = 10.2 Hz, C18-H_AH_B), 5.22 (1H, ddm, *J* = 17.0, 2.1 Hz, C18-H_AH_B), 4.71 (1H, d, *J* = 6.9 Hz, OCH_AH_BO), 4.64 (1H, d, *J* = 6.9 Hz, OCH_AH_BO), 4.33 (1H, dd, *J* = 10.4, 6.8 Hz, C12-H), 3.74 (1H, dd, *J* = 10.1, 6.8 Hz, C11-H), 3.52 (1H, dq, *J* = 2.1, 6.5 Hz, C2-H), 3.31 (1H, t, *J* = 6.0 Hz, C15-H), 3.27 (6H, s, C6-OMe and C13-OMe), 3.05 (1H, d, *J* = 10.4 Hz, C13-H), 2.57-2.52 (2H, m, CH_2SePh), 2.31-2.20 (1H, m with 10 lines, C4-H), 2.12-2.03 (3H, m), 1.64 (1H, t, *J* = 13.2 Hz, C5-H), 1.55-1.45 (1H, m, C3-H), 0.89 (3H, s, C14-Me), 0.84 (3H, d, *J* = 6.5 Hz, C2-Me), 0.73 (3H, s, C14-Me), 0.59 (3H, s, d, *J* = 7.0 Hz, C3-Me).

^{13}C NMR (90 MHz, C_6D_6 referenced to 128.4 ppm): δ = 167.3 (0), 166.0 (0), 137.1 (1), 133.6 (1), 133.3 (1, 2C), 131.4 (0), 130.8 (0), 130.7 (1, 2C), 129.7 (1, 2C), 129.0 (1, 2C), 127.3 (1), 117.0 (2), 99.9 (0), 87.1 (2), 79.6 (1), 78.9 (1), 76.0 (1), 74.5 (1), 72.7 (1), 72.1 (1), 70.9 (1), 61.7 (3), 49.3 (3), 42.1 (0), 35.7 (1), 35.3 (1), 34.1 (2), 32.4 (2), 32.0 (2), 23.1 (3), 18.4 (3), 13.8 (3), 4.6 (3).

LRMS *m/z* (EI) 731 [$M^{+\bullet}$, 0.2%].

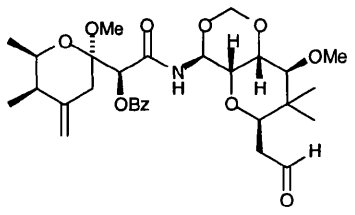
HRMS (EI) Found: $M^{+\bullet}$, 731.2581. $C_{37}H_{49}NO_9Se$ requires *M*, 731.2576.

(1*R*,5*S*,6*S*,8*S*,10*S*)-5{[(2*R*,3*R*,6*S*)-2,3-Dimethyl-2,3-dimethyl-6-methoxy-4-methene-tetrahydro-2*H*-pyran-6-yl]-[(2*S*)-2-benzoylcarbonyloxyethanamido]}-9,9-dimethyl-10-methoxy-8-ethanal-2,4,7-trioxabicyclo[4.4.0]decane 6.23



6.21a
$C_{37}H_{49}NO_9Se$
Mol. Wt.: 730.75

a) Dihydroquinine 9-phenanthryl ether
$K_3Fe(CN)_6$, K_2CO_3, $KOsO_4 \cdot 2H_2O$
^tBuOH, H_2O, rt
b) $NaIO_4$, H_2O, MeOH, rt
c) NEt_3, PhMe, Δ



6.23
$C_{30}H_{41}NO_{10}$
Mol. Wt.: 575.65

Olefin **6.21a** (50 mg, 0.0685 mmol) and hydrquinine 9-phenanthryl ether (2 mg, 0.004 mmol) were dissolved in ^tBuOH (1 mL) to which water (1 mL) was added followed by K_3FeCN_6 (45 mg, 0.14 mmol), K_2CO_3 (20 mg, 0.14 mmol) and potassium osmate dihydrate (1 mg, 0.003 mmol). After stirring at room temperature for 8 h saturated aqueous Na_2SO_4 (2 mL) was added. The mixture was extracted with EtOAc (3 x 15 mL) and the combined organic extracts were dried (Na_2SO_4) and concentrated to give a clear yellow oil.

The yellow oil was dissolved in MeOH (2 mL) to which water (0.65 mL) and sodium metaperiodate (100 mg, 0.047 mmol) were added. The mixture was stirred at room temperature for 1 h then diluted with CH_2Cl_2 (30 mL) and washed with water (2 x 15 mL). The organic phase was dried (Na_2SO_4) to which triethylamine (2 mL) was added before the mixture was concentrated in *vacuo* (12 mm Hg, 18°C) to give a yellow oil.

The yellow oil was dissolved in toluene (1 mL) and triethylamine (1 mL) and heated with a heat gun at reflux for 2 min. The mixture was allowed to cool to room temperature before saturated aqueous $NaHCO_3$ (8 mL) was added. The mixture was extracted with CH_2Cl_2 (3 x 20 mL), the combined organic extracts dried (Na_2SO_4) and concentrated. The yellow oil was purified by column chromatography (SiO_2 6 x 2.5 cm, hexanes:Et_2O 1:1 and 1% Et_3N) to give the desired aldehyde **6.23** (27 mg, 0.0470 mmol, 69%) as a white powder: mp 86-87°C.

$[\alpha]_D^{23}$ +110.3 (*c* 0.3, CH_2Cl_2).

ν_{max} KBr/cm^{-1} 1730 (s), 1701 (s), 1654 (m), 1647 (m), 1270 (m), 1126 (m), 1106 (m), 1037 (m).

^1H NMR assignments made using 2D H-H correlation spectra.

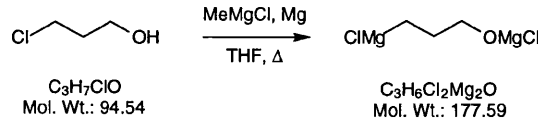
^{1}H NMR (400 MHz, C_6D_6 referenced to 7.16 ppm): δ = 9.72 (1H, d, J = 4.5, C-17-H), 8.38 (2H, dd, J = 8.0, 1.6 Hz), 7.47 (1H, d, J = 9.2 Hz, NH), 7.11-7.00 (3H, m), 5.93 (1H, s, C7-H), 5.91 (1H, t, J = 9.6 Hz, C10-H), 4.94(1H, d, J = 1.6 Hz, =CH_AH_B), 4.85 (1H, J = 1.6 Hz, =CH_AH_B), 4.59 (1H, d, J = 6.8 Hz, OCH_AH_BO), 4.50 (1H, d, J = 6.8 Hz, OCH_AH_BO), 4.26 (1H, dd, J = 10.4, 6.8 Hz, C12-H), 4.02 (1H, dd, J = 10.4, 2.4 Hz, C15-H), 3.81 (1H, dq, J = 2.8, 6.4 Hz, C2-H), 3.77 (1H, dd, J = 9.6, 6.8 Hz, C11-H), 3.27 (3H, s, C13-OMe), 3.09 (1H, d, J = 10.4 Hz, C13-H), 2.91 (1H, d, J = 14.4 Hz, C5-H_AH_B), 2.90 (3H, s, C6-OMe), 2.81 (1H, d, J = 14.4 Hz, C5-H_AH_B), 2.08 (1H, ddd, J = 15.6, 10.4, 4.4 Hz, C16-H_AH_B), 1.93 (1H, dq, J = 2.8, 7.2 Hz, C3-H), 1.82 (1H, dd, J = 16.0, 2.4 Hz, C16-H_AH_B), 0.99 (3H, d, J = 7.2 Hz, C3-Me), 0.86 (3H, d, J = 6.8 Hz, C2-Me), 0.70 (3H, s, C14-Me), 0.64 (3H, s, C14-Me).

^{13}C NMR (100 MHz, C_6D_6 referenced to 128.4 ppm): δ = 200.9 (1), 167.3 (0), 166.1 (0), 145.6, (0), 133.7 (1), 130.8 (1, 2C), 130.7 (0), 129.1 (1, 2C), 111.6 (2), 100.4 (0), 87.3 (2), 79.0 (1), 75.5 (1), 75.0 (1), 75.0 (1), 73.0 (1), 72.7 (1), 70.3 (1), 61.7 (3), 48.4 (3), 44.1 (2), 42.0 (1), 41.5 (0), 35.3 (2), 23.3 (3), 18.0 (3), 13.8 (3), 12.7 (3).

LRMS m/z (EI) 575 [$M^{+\bullet}$, 0.03%], 543 [$(M - OCH_3)^+$, 10%].

HRMS (EI) Found: $M^{+\bullet}$, 575.2734. $C_{30}H_{41}NO_{10}$ requires M, 575.2730.

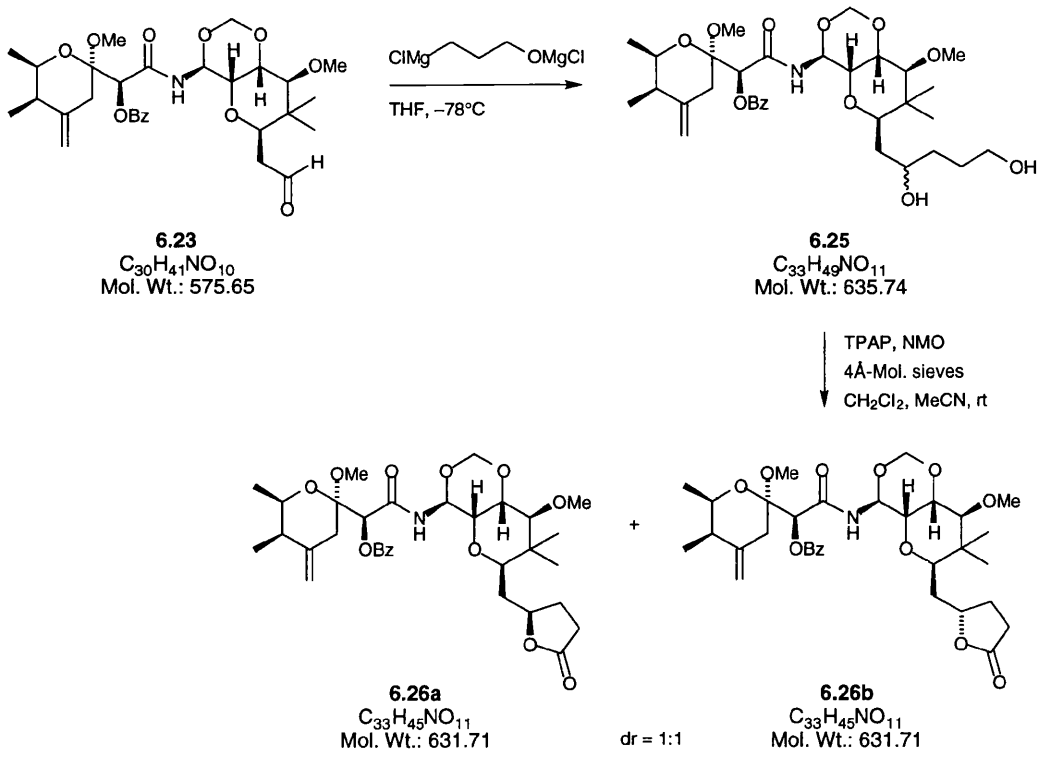
Preparation of Normant Reagent



Prepared according to literature procedure[104].

3-Chloropropan-1-ol (0.9 mL, 8.42 mL) in THF (8.0 mL) was cooled to –20°C to which MeMgCl (3.1 M in THF, 2.72 mL, 8.42 mmol) was added dropwise over 3 min (caution: gas evolution!). After stirring at room temperature for 20 min magnesium (314 mg, 14 mmol) and 1,2-dibromoethane (0.016 mL, 0.19 mmol) were added. The mixture was refluxed for 1 h before another portion of 1,2-dibromoethane (0.016 mL, 0.19 mmol) was added. After refluxing for a further 2 h a homogeneous solution was formed. The mixture was allowed to cool to rt and the concentration was found to be 0.38 M in THF by titration[122].

7-*O*-Benzoyl Theopederin D 6.26a and 17-*epi*-7-*O*-Benzoyl Theopederin D 6.26b.



To a solution of aldehyde **6.23** (15 mg, 0.026 mmol) in THF (0.5 mL) at –78°C was added the Normant reagent (0.30 M in THF, 0.17 mL, 0.052 mmol). After stirring at –78°C for 2 h the reaction was quenched at –78°C by the addition of saturated aqueous $NaHCO_3$ (2 mL) and EtOAc (1 mL). The mixture was stirred and allowed to warm up to room temperature during a 15 min period. The mixture was extracted with EtOAc (3 x 4 mL) and the combined organic extracts were dried (Na_2SO_4) and concentrated. Purification by column chromatography in a Pasteur pipette (SiO_2 0.5 g, hexanes:Et_2O 3:7, Et_2O 100% and EtOAc:Et_2O 1:1) afforded a diastereomeric mixture of diols **6.25** (20 mg) as a white solid.

The diols **6.25** (20 mg) were dissolved in CH_2Cl_2 (0.9 mL) and MeCN (0.1 mL) to which 4-methylmorpholine-*N*-oxide (6 mg, 0.048 mmol), 4Å molecular sieves (16 mg) and TPAP[105] (6 mg, 0.018 mmol) were added at room temperature. After stirring for 0.5 h Et_2O (2 mL) was added and the mixture was concentrated. The residue was purified by filtration through a pad of silica in a Pasteur pipette (SiO_2 0.5 g, EtOAc:CH_2Cl_2 1:1) to give a diastereomeric mixture of lactones **6.26a,b** (14 mg, 0.022 mmol, 85%) as a clear colourless oil. ^1H NMR spectroscopic analysis (C_6D_6, referenced to 7.16 ppm) of the mixture revealed singlets at δ= 5.94 and 5.84 ppm attributed to the C-7 proton corresponding to a 1:1 mixture of diastereoisomeric lactones **6.26a,b**.

The diastereoisomers were separated by preparative TLC. The mixture was divided into six portions and each portion run on a 5 x 20 cm silica gel 60 F-254 plate, eluting with hexanes:EtOAc 1:1 and 1% Et_3N. Two elutions were required for full separation. The top band returned 7-*O*-benzoyl theopederin D **6.26a** (6 mg,

0.0095 mmol, 37%) as a clear colourless oil and the lower band returned 17-*epi*-7-*O*-benzoyl theopederin D **6.26b** (4 mg, 0.0063 mmol, 24%) also as a clear colourless oil.

7-*O*-Benzoyl theopederin D 6.26a

$[\alpha]_D^{23}$ +54.0 (*c* 0.5, EtOAc).

^{1}H NMR assignments made using 2D H-H and C-H correlation spectra.

^{1}H NMR (400 MHz, C_6D_6 referenced to 7.16 ppm): δ = 8.30-8.20 (2H, m), 7.27 (1H, d, *J* = 9.6 Hz, NH), 7.11-7.00 (3H, m), 5.84 (1H, s, C7-H), 5.76 (1H, t, *J* = 9.6 Hz, C10-H), 4.83-4.77 (2H, m, $=CH_2$), 4.57 (1H, d, *J* = 7.2 Hz, OCH_AH_BO), 4.60-4.50 (1H, m, C17-H), 4.50 (1H, d, *J* = 7.2 Hz, OCH_AH_BO), 4.23 (1H, dd, *J* = 10.4, 6.8 Hz, C12-H), 3.81 (1H, dq, *J* = 2.4, 6.4 Hz, C2-H), 3.66 (1H, dd, *J* = 9.6, 6.8 Hz, C11-H), 3.26 (3H, s, C13-OMe), 3.15 (1H, d, *J* = 10.4 Hz, C15-H), 2.93 (1H, d, *J* = 12.4 Hz, C13-H), 2.92 (3H, s, C6-OMe), 2.78 (1H, bd, *J* = 13.6 Hz, C5-H_AH_B), 2.72 (1H, d, *J* = 14.0 Hz, C5-H_AH_B), 2.50-2.35 (1H, m), 2.36 (1H, dt, *J* = 17.2, 9.6 Hz, C19-H_AH_B), 2.18-2.08 (1H, m, C16-H_AH_B), 1.90 (1H, dq, *J* = 2.8, 7.2 Hz, C3-H), 1.92-1.82 (1H, m, C16-H_AH_B), 1.13-1.15 (2H, m, C18-H_2), 1.03 (3H, d, *J* = 6.8 Hz, C3-Me), 0.90 (3H, d, *J* = 6.4 Hz, C2-Me), 0.75 (3H, s, C14-Me), 0.68 (3H, s, C14-Me).

^{13}C NMR (100 MHz, C_6D_6 referenced to 128.4 ppm): δ = 176.4 (0), 167.4 (0), 165.8 (0), 145.3 (0), 134.0 (1), 130.5 (1, 2C), 130.2 (0), 129.3 (1, 2C), 111.9 (2), 100.1 (0), 86.9 (2), 79.1 (1), 78.4 (1), 75.5 (1), 75.3 (1), 74.5 (1), 73.4 (1), 72.4 (1), 70.3 (1), 61.7 (3), 48.8 (3), 41.8 (1), 41.6 (0), 36.0 (2), 35.0 (2), 29.2 (2), 28.6 (2), 23.2 (3), 18.0 (3), 14.7 (3), 12.6 (3)

LRMS *m/z* (CI) 649 [$(M+NH_4)^+$, 20%], 617 [$(M+NH_4-OCH_3)^+$, 75%], 600 [$(M-OCH_3)^+$, 10%].

HRMS (CI) Found: $(M+NH_4)^+$, 649.3339. $C_{33}H_{49}N_2O_{11}$ requires *M*, 649.3336.

17-*epi*-7-*O*-Benzoyl theopederin D 6.26b

$[\alpha]_D^{21}$ +71.3 (*c* 0.3, EtOAc).

^{1}H NMR assignments made using 2D H-H correlation spectra.

^{1}H NMR (400 MHz, C_6D_6 referenced to 7.16 ppm): δ = 8.30-8.20 (2H, m), 7.12 (1H, d, *J* = 9.2 Hz, NH), 7.09-7.02 (3H, m), 5.94 (1H, s, C7-H), 5.77 (1H, t, *J* = 9.2 Hz, C10-H), 4.80 (2H, dm, *J* = 9.7 Hz, $=CH_2$), 4.64 (2H, s, OCH_2O), 4.55 (1H, ddd, *J* = 15.2, 9.2, 3.2 Hz, C17-H), 4.24 (1H, dd, *J* = 10.0, 6.8 Hz, C12-H), 3.90 (1H, dd, *J* = 9.6, 6.8 Hz, C11-H), 3.83 (1H, dq, *J* = 2.8, 6.4 Hz, C2-H), 3.51 (1H, dd, *J* = 8.8, 0.8 Hz, C15-H), 3.28 (3H, s, OMe),3.04 (3H, s, OMe), 2.99 (1H, d, *J* = 10.0 Hz, C13-H), 2.85 (1H, bd, *J* = 14.4 Hz, C5-H_AH_B), 2.78 (1H,

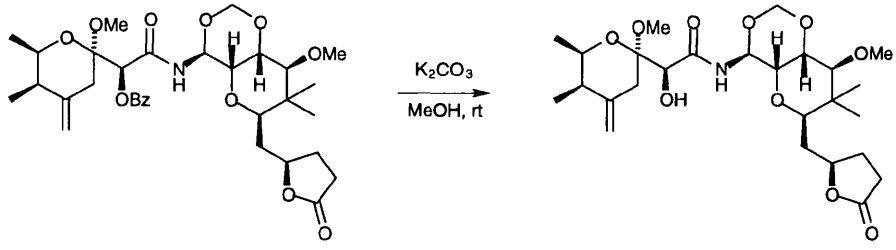
d, J = 14.0 Hz, C5-H_AH_B), 2.27 (1H, dt, J = 17.6, 9.6 Hz, C19-H_AH_B), 2.04 (1H, ddd, J = 17.2, 9.2, 3.2 Hz, C19-H_AH_B), 1.95 (1H, dq, J = 2.8, 7.2 Hz, C3-H), 1.74 (1H, dddd, J = 12.8, 10.0, 6.4, 3.6 Hz, C18-H_AH_B), 1.42 (1H, ddd, J = 14.4, 8.8, 1.6 Hz, C16-H_AH_B), 1.30-1.10 (2H, m, C16-H_AH_B) and C18-H_AH_B), 1.02 (3H, d, J = 7.2 Hz, C3-Me), 0.92 (3H, d, J = 6.8 Hz, C2-Me), 0.79 (3H, s, C14-Me), 0.78 (3H, s, C14-Me).

^{13}C NMR (100 MHz, C_6D_6 referenced to 128.4 ppm): δ = 176.0 (0), 167.1 (0), 166.1 (0), 146.5 (0), 133.8 (1), 130.6 (1, 2C), 130.4 (0), 129.2 (1, 2C), 111.2 (2), 100.1 (0), 87.1 (2), 79.4 (1), 78.0 (1), 76.2 (1), 75.4 (1), 75.2 (1), 73.7 (1), 71.4 (1), 70.1 (1), 61.7 (3), 48.9 (3), 42.0 (1), 41.5 (0), 36.3 (2), 35.3 (2), 29.3 (2), 29.1 (2), 23.4 (3), 18.1 (3), 14.7 (3), 12.8 (3)

LRMS m/z (EI) 600 [$(M-OCH_3)^+$, 10%].

HRMS (CI) Found: $(M+NH_4)^+$, 649.3331. $C_{33}H_{49}N_2O_{11}$ requires M, 649.3336.

Theopederin D 1.1d



6.26a
$C_{33}H_{45}NO_{11}$
Mol. Wt.: 631.71

1.1d Theopederin D
$C_{26}H_{41}NO_{10}$
Mol. Wt.: 527.60

Potassium carbonate (1 mg, 0.007 mmol) was added to a solution of 7-*O*-benzoyl theopederin D **6.26a** (3 mg, 0.0048 mmol) in anhydrous MeOH (0.3 mL) at room temperature. The mixture was stirred for 1 h before the addition of H_2O (3 mL). The mixture was then extracted with EtOAc (3 x 6 mL) and the combined organic extracts washed with brine (2 mL), dried (Na_2SO_4) and concentrated. The residue was purified by filtration through a pad of silica in a Pasteur pipette (SiO_2 0.5 g, hexanes:EtOAc 1:1) to give theopederin D **1.1d** (2 mg, 0.0038 mmol, 79%) as a white solid: mp = 87-88°C.

Synthetic theopederin D: $[\alpha]_D^{23}$ +86.2 (c 0.1, $CHCl_3$).

Natural theopederin D: literature value[1] $[\alpha]_D$ +80 (c 0.04, $CHCl_3$).

The ^{1}H and ^{13}C NMR spectra were compared with those reported in the literature[1] and are shown below.

^{1}H NMR (400 MHz, $CDCl_3$ referenced to 7.24 ppm)

No.	Natural	Synthetic
9-NH	7.52 d, 9.4	7.51 d, 10.3
10	5.81 dd, 9.4, 9.4	5.80 dd, 9.5
10-OCH_2	5.13 d, 7.0	5.11 d, 7.0
	4.87 d, 7.0	4.86 d, 7.0
4=CH_2	4.86 bs	4.84 t,
	4.74 bs	4.73 t, 1.7
17	4.45 ddd, 14.2, 8.4, 6.0	4.42 ddd, 14.1, 8.2, 5.9
7	4.27 d, 3.1	4.25 d, 3.2
12	4.21 dd, 10.2, 6.4	4.19, d, 9.7, 6.4
7-OH	4.08 d, 3.1	4.11 d, 3.2
2	4.03 dq, 2.7, 6.5	4.01 dq, 2.8, 6.6
11	3.82 dd, 9.4, 6.4	3.80 dd, 9.2, 6.4
13-OMe	3.56 s	3.54 s
13	3.44 d, 10.2	3.42 d, 9.5
15	3.42 d, 10.2	3.40 d, 9.0
6-OMe	3.28 s	3.28 s
19	2.51 ddd, 17.6, 10.0, 3.8	2.55-2.48 m
	2.45 dd, 17.6, 11.1	2.46 dd, 18.0, 10.3
18	2.40 m	2.41-2.35 m
5	2.35 d, 14.0	2.33 d, 13.9
3	2.26 dq, 2.7, 7.1	2.24 dq 2.6, 7.1
5	2.21 bd, 14.0	2.18 d, 14.1
16	1.94 m	1.97-1.87 m
18	1.75 m	1.80-1.68 m
16	1.59 dd, 14.2, 8.3	1.58 ddd, 14.3, 8.3, 1.3
2-Me	1.20 d, 6.5	1.18 d, 6.6
14-Me	1.02 s	1.00 s
3-Me	1.01 d, 7.1	0.98 d, 7.1
14-Me	0.88 s	0.86 s

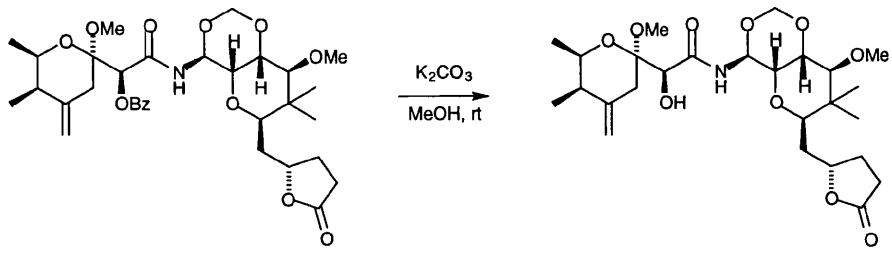
^{13}C NMR (100 MHz, $CDCl_3$ referenced to 77.0 ppm):

No.	Natural	Synthetic
20	176.7 (0)	177.5 (0)

8	171.7 (0)	172.3 (0)
4	144.6 (0)	145.0 (0)
4=CH_2	111.0 (2)	111.0 (2)
6	99.7 (0)	99.8 (0)
10-OCH_2	86.4 (2)	86.5 (2)
13	79.2 (1)	79.5 (1)
17	79.1 (1)	79.2 (1)
15	75.8 (1)	76.0 (1)
12	73.9 (1)	74.0 (1)
10	73.4 (1)	73.6 (1)
7	71.5 (1)	71.6 (1)
11	70.0 (1)	69.5 (1)
2	69.4 (1)	69.5 (1)
13-OMe	61.4 (3)	61.7 (3)
6-OMe	48.2 (3)	48.5 (3)
3	41.1 (1)	41.3 (1)
14	41.1 (0)	41.1 (0)
16	34.6 (2)	35.0 (2)
5	32.9 (2)	33.3 (2)
19	28.1 (2)	28.7 (2)
18	27.6 (2)	28.0 (2)
14-Me_{eq}	23.0 (3)	22.6 (3)
2-Me	17.4 (3)	18.0 (3)
14-Me_{ax}	13.5 (3)	14.1 (3)
3-Me	11.5 (3)	12.0 (3)

LRMS *m/z* (CI) 496 [$(M–OCH_3)^+$, 100%], 513 [$(M–OCH_3+NH_4)^+$, 10%].

17-*epi*-Theopederin D 6.27



6.26b
$C_{33}H_{45}NO_{11}$
Mol. Wt.: 631.71

6.27
$C_{26}H_{41}NO_{10}$
Mol. Wt.: 527.60

Potassium carbonate (1 mg, 0.007 mmol) was added to a solution of 17-*epi*-7-*O*-benzoyl theopederin D **6.26b** (2 mg, 0.0032 mmol) in anhydrous MeOH (0.3 mL) at room temperature. The mixture was stirred for 1 h before the addition of H_2O (3 mL). The mixture was extracted with EtOAc (3 x 6 mL) and the combined organic extracts washed with brine (2 mL), dried (Na_2SO_4) and concentrated. The residue was purified by filtration through a pad of silica in a Pasteur pipette (SiO_2 0.5 g, hexanes:EtOAc 1:1) to give 17-*epi*-theopederin D **6.27** (1 mg, 0.0019 mmol, 59%) as a white solid: mp = 80-82°C.

$[\alpha]_D^{23}$ +43.2 (*c* 0.2, CH_2Cl_2).

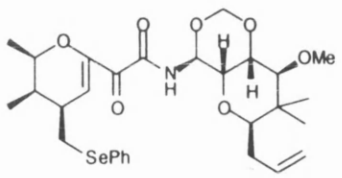
^{1}H NMR (400 MHz, $CDCl_3$ referenced to 7.24 ppm): δ = 7.41 (1H, d, *J* = 9.4 Hz, NH), 5.83 (1H, t, *J* = 9.2 Hz, C10-H), 5.12 (1H, d, *J* = 7.0 Hz, OCH_AH_BO), 4.87 (1H, d, *J* = 6.8 Hz, OCH_AH_BO), 4.87 (1H, t, *J* = 2.0 Hz, $=CH_AH_B$), 4.75 (1H, *J* = 1.7 Hz, $=CH_AH_B$), 4.48 (1H, ddd, *J* 12.1, 9.1, 6.4, C17-H), 4.26 (1H, d, *J* = 2.4 Hz, C7-H), 4.19 (1H, dd, *J* = 9.7, 6.5 Hz, C12-H), 4.05 (1H, dq, *J* = 2.8, 6.6 Hz, C2-H), 3.83 (1H, d, *J* = 2.5 Hz, C7-OH), 3.82 (1H, dd, *J* = 9.0, 6.5 Hz, C11-H), 3.65 (1H, dd, *J* = 9.8, 1.5 Hz, C15-H), 3.54 (3H, s, OMe), 3.44 (1H, d, *J* = 9.7 Hz, C13-H), 3.30 (3H, s, OMe), 2.49-2.42 (2H, m, C19-H_2), 2.36 (1H, d, *J* = 13.9 Hz, C5-H), 2.28 (1H, dq, *J* = 2.7, 7.1 Hz, C3-H), 2.22-2.17 (1H, m, C18-H_AH_B), 2.16 (1H, dm, *J* = 14.1 Hz, C5-H), 1.83-1.70 (2H, m, C16-H_AH_B and C18-H_AH_B), 1.60 (1H, dd, *J* = 9.7, 3.0 Hz, C16-H_AH_B), 1.19 (3H, d, *J* = 6.6 Hz, C2-Me), 1.02 (3H, s, C14-Me), 0.99 (3H, d, *J* = 7.1 Hz, C3-Me), 0.84 (3H, s, C14-Me).

^{13}H NMR (100 MHz, $CDCl_3$ referenced to 77.0ppm): δ = 176.5 (0), 171.5 (0), 145.4 (0), 111.1 (2), 99.8 (0), 86.5 (2), 79.5 (1), 78.1 (1), 77.2 (1), 76.0 (1), 74.2 (1), 74.05 (1), 71.5 (1), 69.4 (1), 61.7 (3), 48.7 (3), 41.2 (1), 40.9 (0), 35.4 (2), 33.3 (2), 29.0 (2), 28.7 (2), 22.7 (3), 18.0 (3), 14.1 (3), 12.5 (3).

LRMS *m/z* (CI) 496 [$(M-OCH_3)^+$, 100%].

HRMS (EI) Found: $(M-OCH_3)^+$, 496.2516. $C_{25}H_{38}NO$ requires *M*, 496.2546.

Appendix A X-ray data for intermediate 6.20



6.20 (mp = 144-145°C)

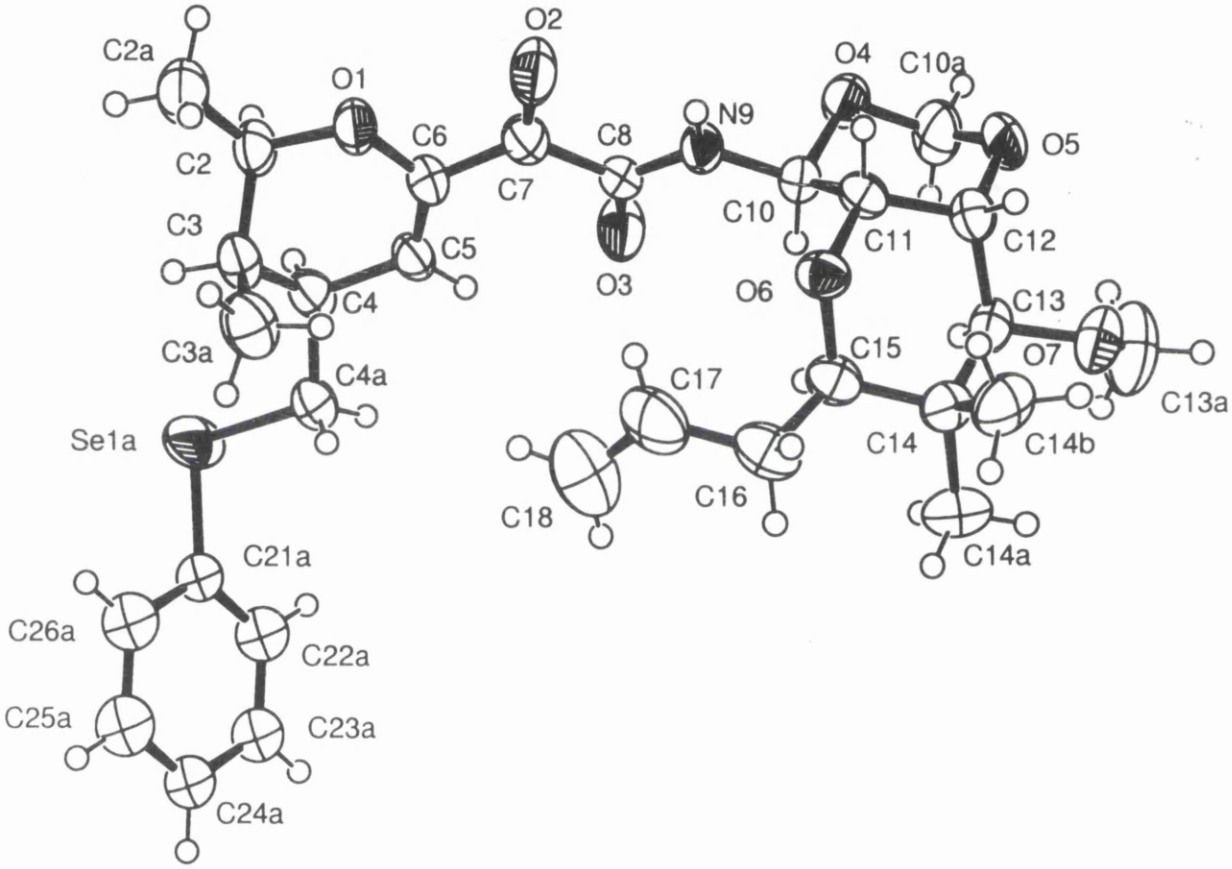


Table 1. Crystal data and structure refinement for pk3.

Identification code	pk3
Empirical formula	C29 H39 N O7 Se
Formula weight	592.57
Temperature	291(2) K
Wavelength	0.71073 A
Crystal system, space group	Monoclinic, P 21
Unit cell dimensions	a = 8.5035(5) A alpha = 90 deg. b = 10.0704(9) A beta = 103.768(3) deg. c = 17.6777(6) A gamma = 90 deg.
Volume	1470.31(17) A^3
Z, Calculated density	2, 1.338 Mg/m^3
Absorption coefficient	1.321 mm^-1
F(000)	620
Crystal size	0.30 x 0.23 x 0.07 mm
Theta range for data collection	2.34 to 25.97 deg.
Limiting indices	-1<=h<=10, -1<=k<=12, -21<=l<=21
Reflections collected / unique	4104 / 3402 [R(int) = 0.0234]
Completeness to theta = 25.97	99.9 %
Absorption correction	Psi-scan
Max. and min. transmission	0.8306 and 0.6815
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3402 / 1 / 332
Goodness-of-fit on F^2	1.001
Final R indices [I>2sigma(I)]	R1 = 0.0361, wR2 = 0.0626
R indices (all data)	R1 = 0.1014, wR2 = 0.0774
Absolute structure parameter	-0.010(11)
Largest diff. peak and hole	0.233 and -0.269 e.A^-3

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for pk3.
U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
C(2)	-10681(5)	-2110(6)	-1918(2)	48(1)
C(2A)	-11671(6)	-1151(7)	-1575(3)	69(2)
C(3)	-8910(5)	-2231(6)	-1513(2)	49(1)
C(3A)	-7969(6)	-941(7)	-1498(3)	67(2)
C(4)	-8211(5)	-3358(6)	-1916(2)	46(1)
C(4A)	-6387(5)	-3587(7)	-1637(2)	59(2)
C(5)	-8665(5)	-3094(6)	-2789(2)	42(1)
C(6)	-9891(5)	-2314(6)	-3110(2)	43(1)
C(7)	-10395(6)	-1934(6)	-3945(2)	48(1)
C(8)	-9614(5)	-2569(6)	-4567(2)	40(1)
C(10)	-9320(5)	-2167(6)	-5883(2)	42(1)
C(10A)	-9810(6)	-3185(7)	-7086(3)	66(2)
C(11)	-9029(5)	-858(6)	-6262(2)	39(1)
C(12)	-8524(5)	-1082(6)	-7029(2)	45(1)
C(13)	-6743(5)	-1410(6)	-6918(2)	44(1)
C(13A)	-6015(8)	-2590(8)	-7959(3)	100(2)
C(14)	-5654(5)	-446(6)	-6346(3)	45(1)
C(14A)	-3904(5)	-941(7)	-6191(3)	64(2)
C(14B)	-5755(5)	969(7)	-6683(3)	63(1)
C(15)	-6255(5)	-463(6)	-5595(2)	47(1)
C(16)	-5360(5)	423(6)	-4928(3)	62(2)
C(17)	-5978(7)	205(8)	-4206(3)	82(2)
C(18)	-5209(9)	-337(8)	-3580(4)	108(3)
C(21A)	-3654(5)	-3849(10)	-278(5)	45(5)
C(22A)	-2493(10)	-4523(9)	-565(5)	60(4)
C(23A)	-861(8)	-4234(12)	-279(6)	57(3)
C(24A)	-390(7)	-3272(14)	294(5)	53(3)
C(25A)	-1552(13)	-2599(11)	581(4)	68(3)
C(26A)	-3184(11)	-2887(9)	295(5)	64(3)
C(21B)	-3585(7)	-3673(14)	-243(7)	51(8)
C(22B)	-2669(15)	-2869(11)	336(6)	45(4)
C(23B)	-988(15)	-2927(13)	504(5)	34(3)
C(24B)	-223(7)	-3789(17)	92(7)	49(3)
C(25B)	-1139(14)	-4594(15)	-488(7)	67(5)
C(26B)	-2820(13)	-4536(13)	-655(7)	65(6)
N(9)	-9987(5)	-1904(6)	-5230(2)	44(1)
O(1)	-10863(4)	-1674(5)	-2716(2)	50(1)
O(2)	-11448(5)	-1131(5)	-4168(2)	75(1)
O(3)	-8773(4)	-3561(5)	-4453(2)	66(1)
O(4)	-10482(3)	-2903(5)	-6452(2)	55(1)
O(5)	-9583(4)	-2028(5)	-7499(2)	60(1)
O(6)	-7922(3)	-38(4)	-5749(2)	44(1)
O(7)	-6335(4)	-1366(5)	-7658(2)	62(1)
Se(1A)	-5884(10)	-4223(5)	-569(5)	79(2)
Se(1B)	-5878(14)	-3743(13)	-464(5)	81(2)

Table 3. Bond lengths [A] and angles [deg] for pk3.

C(2)-O(1)	1.450(5)
C(2)-C(2A)	1.501(7)
C(2)-C(3)	1.510(6)
C(3)-C(3A)	1.523(7)
C(3)-C(4)	1.534(6)
C(4)-C(5)	1.522(5)
C(4)-C(4A)	1.529(5)
C(4A)-Se(1A)	1.942(8)
C(4A)-Se(1B)	2.020(10)
C(5)-C(6)	1.321(6)
C(6)-O(1)	1.364(5)
C(6)-C(7)	1.485(6)
C(7)-O(2)	1.200(5)
C(7)-C(8)	1.551(6)
C(8)-O(3)	1.217(6)
C(8)-N(9)	1.323(6)
C(10)-N(9)	1.427(5)
C(10)-O(4)	1.436(5)
C(10)-C(11)	1.525(7)
C(10A)-O(4)	1.403(5)
C(10A)-O(5)	1.412(6)
C(11)-O(6)	1.409(5)
C(11)-C(12)	1.533(6)
C(12)-O(5)	1.433(5)
C(12)-C(13)	1.516(6)
C(13)-O(7)	1.431(5)
C(13)-C(14)	1.542(6)
C(13A)-O(7)	1.395(7)
C(14)-C(15)	1.532(6)
C(14)-C(14A)	1.531(6)
C(14)-C(14B)	1.539(7)
C(15)-O(6)	1.444(5)
C(15)-C(16)	1.530(6)
C(16)-C(17)	1.506(7)
C(17)-C(18)	1.268(8)
C(21A)-C(22A)	1.3900
C(21A)-C(26A)	1.3900
C(21A)-Se(1A)	1.881(9)
C(22A)-C(23A)	1.3900
C(23A)-C(24A)	1.3900
C(24A)-C(25A)	1.3900
C(25A)-C(26A)	1.3900
C(21B)-C(22B)	1.3900
C(21B)-C(26B)	1.3900
C(21B)-Se(1B)	1.897(13)
C(22B)-C(23B)	1.3900
C(23B)-C(24B)	1.3900
C(24B)-C(25B)	1.3900
C(25B)-C(26B)	1.3900

O(1)-C(2)-C(2A)	105.0(4)
O(1)-C(2)-C(3)	110.4(3)
C(2A)-C(2)-C(3)	116.9(4)
C(2)-C(3)-C(3A)	113.6(4)
C(2)-C(3)-C(4)	107.0(4)
C(3A)-C(3)-C(4)	112.3(4)
C(5)-C(4)-C(4A)	110.3(3)
C(5)-C(4)-C(3)	108.0(4)
C(4A)-C(4)-C(3)	115.9(4)
C(4)-C(4A)-Se(1A)	109.6(4)

C(4)-C(4A)-Se(1B)	107.2(4)
Se(1A)-C(4A)-Se(1B)	14.8(4)
C(6)-C(5)-C(4)	121.6(4)
C(5)-C(6)-O(1)	125.0(4)
C(5)-C(6)-C(7)	126.3(4)
O(1)-C(6)-C(7)	108.6(4)
O(2)-C(7)-C(6)	121.1(4)
O(2)-C(7)-C(8)	117.2(4)
C(6)-C(7)-C(8)	121.7(5)
O(3)-C(8)-N(9)	124.7(4)
O(3)-C(8)-C(7)	123.8(4)
N(9)-C(8)-C(7)	111.5(5)
N(9)-C(10)-O(4)	108.8(4)
N(9)-C(10)-C(11)	109.4(4)
O(4)-C(10)-C(11)	107.1(3)
O(4)-C(10A)-O(5)	112.2(5)
O(6)-C(11)-C(10)	112.1(3)
O(6)-C(11)-C(12)	111.7(4)
C(10)-C(11)-C(12)	111.8(4)
O(5)-C(12)-C(13)	113.6(4)
O(5)-C(12)-C(11)	109.9(4)
C(13)-C(12)-C(11)	113.5(3)
O(7)-C(13)-C(12)	109.1(3)
O(7)-C(13)-C(14)	110.0(4)
C(12)-C(13)-C(14)	111.9(4)
C(15)-C(14)-C(14A)	110.5(4)
C(15)-C(14)-C(13)	106.8(4)
C(14A)-C(14)-C(13)	108.6(4)
C(15)-C(14)-C(14B)	110.3(4)
C(14A)-C(14)-C(14B)	109.5(4)
C(13)-C(14)-C(14B)	111.1(4)
O(6)-C(15)-C(16)	105.0(4)
O(6)-C(15)-C(14)	110.3(3)
C(16)-C(15)-C(14)	117.0(4)
C(17)-C(16)-C(15)	111.0(4)
C(18)-C(17)-C(16)	126.2(6)
C(22A)-C(21A)-C(26A)	120.0
C(22A)-C(21A)-Se(1A)	124.1(5)
C(26A)-C(21A)-Se(1A)	115.8(5)
C(23A)-C(22A)-C(21A)	120.0
C(24A)-C(23A)-C(22A)	120.0
C(23A)-C(24A)-C(25A)	120.0
C(26A)-C(25A)-C(24A)	120.0
C(25A)-C(26A)-C(21A)	120.0
C(22B)-C(21B)-C(26B)	120.0
C(22B)-C(21B)-Se(1B)	122.8(7)
C(26B)-C(21B)-Se(1B)	117.1(7)
C(23B)-C(22B)-C(21B)	120.0
C(22B)-C(23B)-C(24B)	120.0
C(23B)-C(24B)-C(25B)	120.0
C(24B)-C(25B)-C(26B)	120.0
C(25B)-C(26B)-C(21B)	120.0
C(8)-N(9)-C(10)	124.5(5)
C(6)-O(1)-C(2)	114.7(4)
C(10A)-O(4)-C(10)	108.7(3)
C(10A)-O(5)-C(12)	113.2(3)
C(11)-O(6)-C(15)	115.0(3)
C(13A)-O(7)-C(13)	115.7(4)
C(21A)-Se(1A)-C(4A)	100.1(5)
C(21B)-Se(1B)-C(4A)	99.6(6)

Symmetry transformations used to generate equivalent atoms:

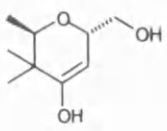
Table 4. Anisotropic displacement parameters (A^2 x 10^3) for pk3.
The anisotropic displacement factor exponent takes the form:
-2 pi^2 [h^2 a*^2 U11 + ... + 2 h k a* b* U12]

	U11	U22	U33	U23	U13	U12
C(2)	57(3)	54(4)	34(2)	8(2)	13(2)	2(3)
C(2A)	75(4)	84(5)	49(3)	6(3)	20(3)	20(4)
C(3)	60(3)	52(4)	33(2)	-2(2)	8(2)	-5(3)
C(3A)	81(4)	62(4)	56(3)	-7(3)	9(3)	-9(4)
C(4)	48(3)	51(4)	36(2)	4(2)	2(2)	-1(3)
C(4A)	54(3)	84(5)	35(2)	10(3)	5(2)	8(3)
C(5)	43(2)	47(3)	33(2)	-4(2)	3(2)	-1(3)
C(6)	46(3)	50(3)	32(2)	-4(2)	7(2)	-2(3)
C(7)	46(3)	57(4)	38(3)	1(3)	7(2)	9(3)
C(8)	34(2)	49(4)	35(2)	-1(3)	4(2)	0(3)
C(10)	38(3)	56(4)	34(2)	2(3)	10(2)	3(3)
C(10A)	80(4)	76(5)	46(3)	-24(3)	20(3)	-25(3)
C(11)	38(3)	36(3)	40(3)	3(2)	2(2)	4(2)
C(12)	48(3)	49(4)	38(2)	7(3)	8(2)	1(3)
C(13)	51(3)	45(3)	41(2)	7(2)	19(2)	8(3)
C(13A)	158(6)	87(6)	73(4)	1(4)	62(4)	25(5)
C(14)	43(3)	41(3)	53(3)	7(3)	12(2)	2(3)
C(14A)	43(3)	56(4)	91(4)	0(3)	11(3)	0(3)
C(14B)	62(3)	54(4)	78(3)	20(4)	25(2)	-2(4)
C(15)	45(3)	42(3)	50(3)	0(2)	5(2)	-1(3)
C(16)	62(3)	52(4)	63(3)	-15(3)	-3(3)	-11(3)
C(17)	86(4)	84(5)	65(4)	-28(4)	-2(3)	-16(4)
C(18)	135(6)	103(7)	76(4)	-10(5)	7(4)	-5(5)
N(9)	46(2)	52(3)	34(2)	8(2)	12(2)	12(2)
O(1)	56(2)	61(2)	34(2)	1(2)	13(2)	10(2)
O(2)	81(3)	107(4)	43(2)	19(2)	26(2)	51(3)
O(3)	80(2)	72(3)	49(2)	12(2)	23(2)	32(2)
O(4)	54(2)	69(3)	45(2)	-11(2)	16(2)	-20(2)
O(5)	61(2)	84(3)	30(2)	-12(2)	3(2)	-16(2)
O(6)	38(2)	45(2)	47(2)	-9(2)	6(1)	0(2)
O(7)	76(2)	66(3)	52(2)	9(2)	33(2)	4(2)
Se(1A)	59(2)	108(3)	60(2)	39(2)	-2(2)	-9(2)
Se(1B)	60(2)	144(7)	37(1)	15(3)	7(1)	22(4)

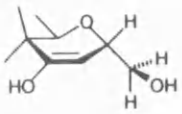
Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3) for pk3.

	x	y	z	U(eq)
H(2)	-11175	-2990	-1928	57
H(2A1)	-11579	-1367	-1037	83
H(2A2)	-12785	-1208	-1854	83
H(2A3)	-11282	-264	-1614	83
H(3)	-8838	-2498	-973	59
H(3A1)	-6920	-1032	-1151	81
H(3A2)	-8546	-231	-1323	81
H(3A3)	-7847	-746	-2013	81
H(4)	-8753	-4181	-1824	56
H(4A1)	-5813	-2764	-1667	70
H(4A2)	-6039	-4235	-1969	70
H(5)	-8066	-3493	-3103	51
H(10)	-8307	-2667	-5721	51
H(10A)	-10518	-3790	-7437	80
H(10B)	-8775	-3624	-6899	80
H(11)	-10066	-385	-6391	47
H(12)	-8701	-237	-7312	54
H(13)	-6556	-2313	-6710	53
H(13A)	-5060	-2970	-7629	120
H(13B)	-5848	-2467	-8473	120
H(13C)	-6917	-3176	-7984	120
H(14A)	-3584	-1008	-6675	77
H(14B)	-3827	-1798	-5947	77
H(14C)	-3205	-328	-5854	77
H(14D)	-5758	928	-7225	76
H(14E)	-4838	1475	-6410	76
H(14F)	-6733	1388	-6622	76
H(15)	-6198	-1380	-5404	56
H(16A)	-4210	228	-4814	74
H(16B)	-5509	1347	-5084	74
H(17)	-7023	496	-4222	98
H(18A)	-4159	-644	-3536	129
H(18B)	-5694	-428	-3163	129
H(22A)	-2807	-5166	-948	72
H(23A)	-83	-4685	-471	68
H(24A)	702	-3079	486	63
H(25A)	-1237	-1955	965	82
H(26A)	-3961	-2436	487	77
H(22B)	-3180	-2292	611	54
H(23B)	-375	-2389	891	41
H(24B)	901	-3828	204	59
H(25B)	-628	-5171	-763	80
H(26B)	-3433	-5074	-1043	78
H(9)	-10560(50)	-1230(50)	-5260(30)	45(17)

Appendix B results of MM2 calculations for intermediate C

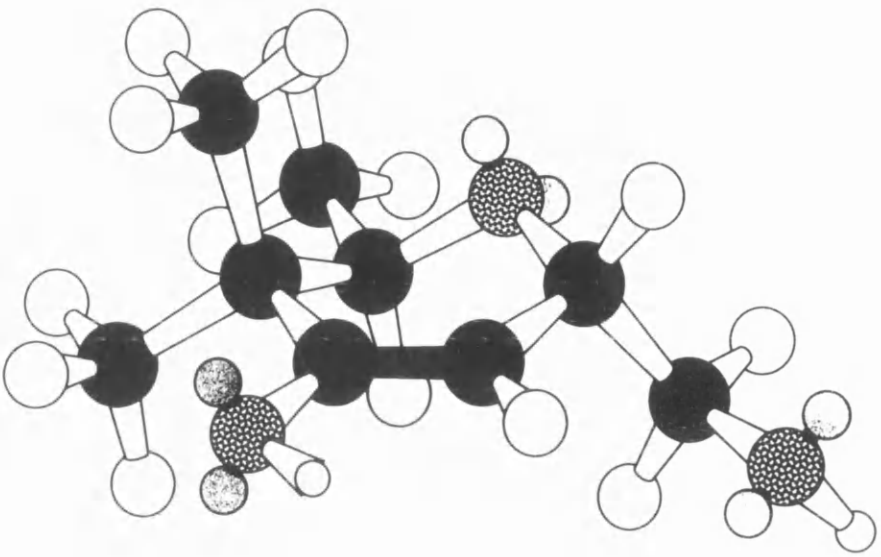


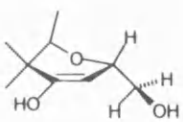
C



MM2: 12.5 Kcal/mole

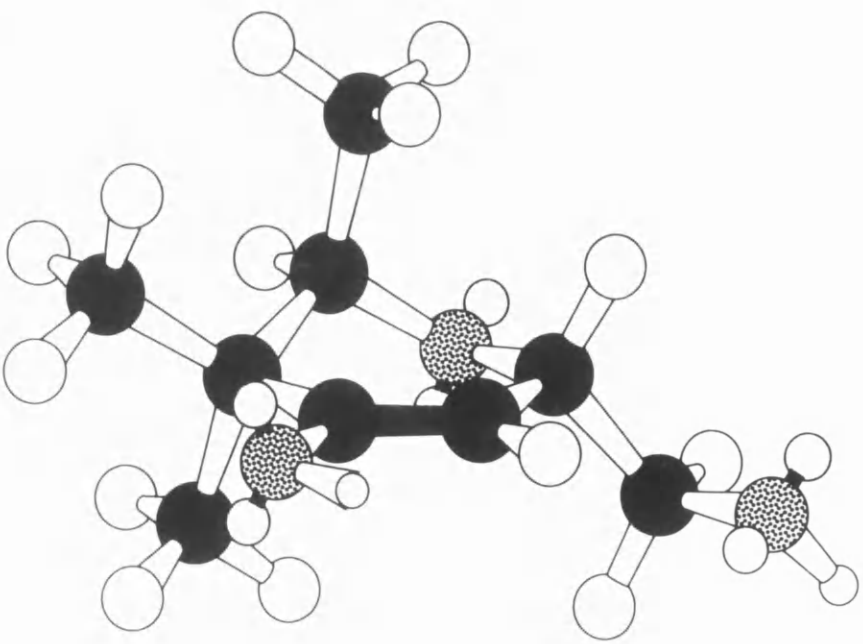
D



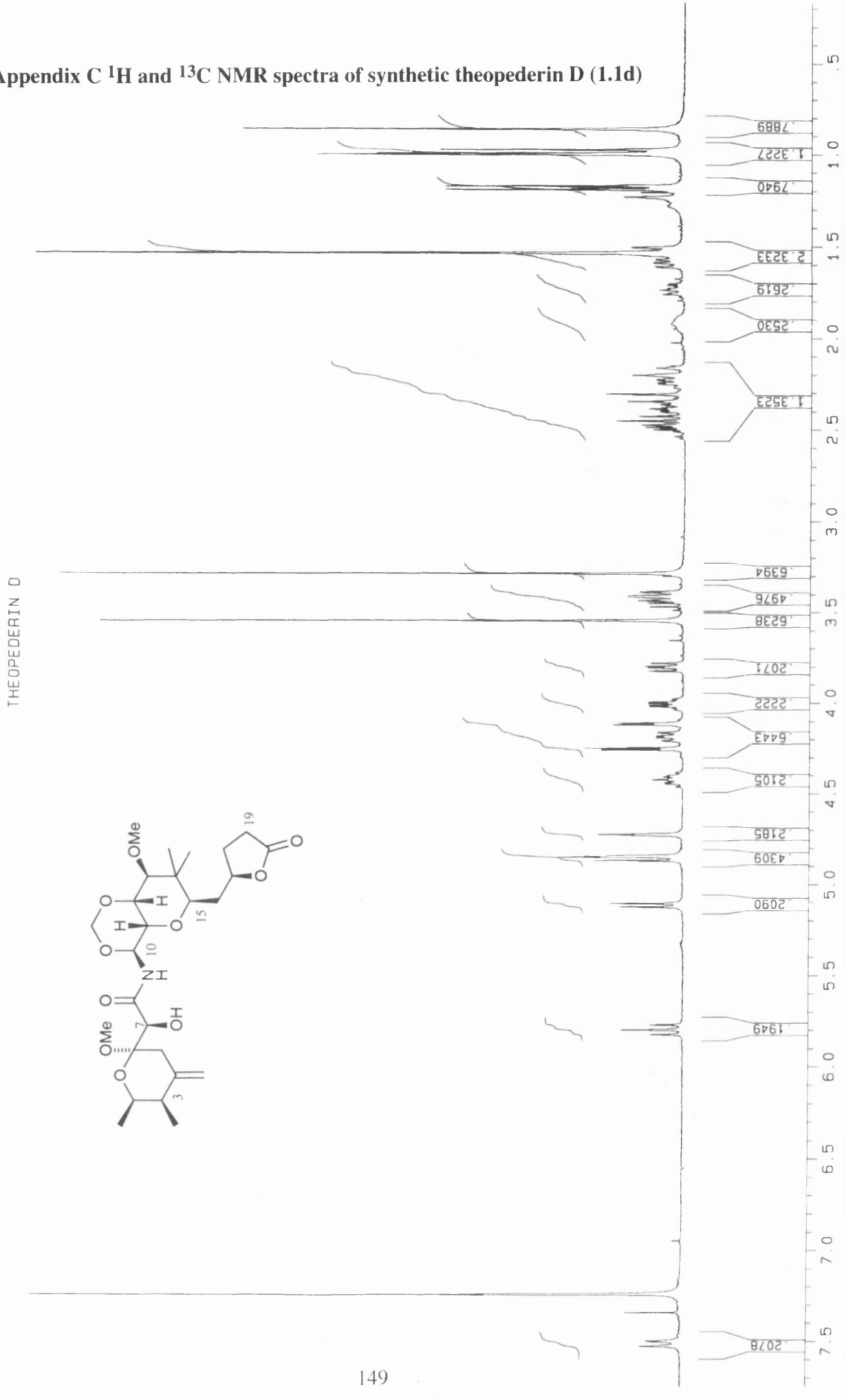


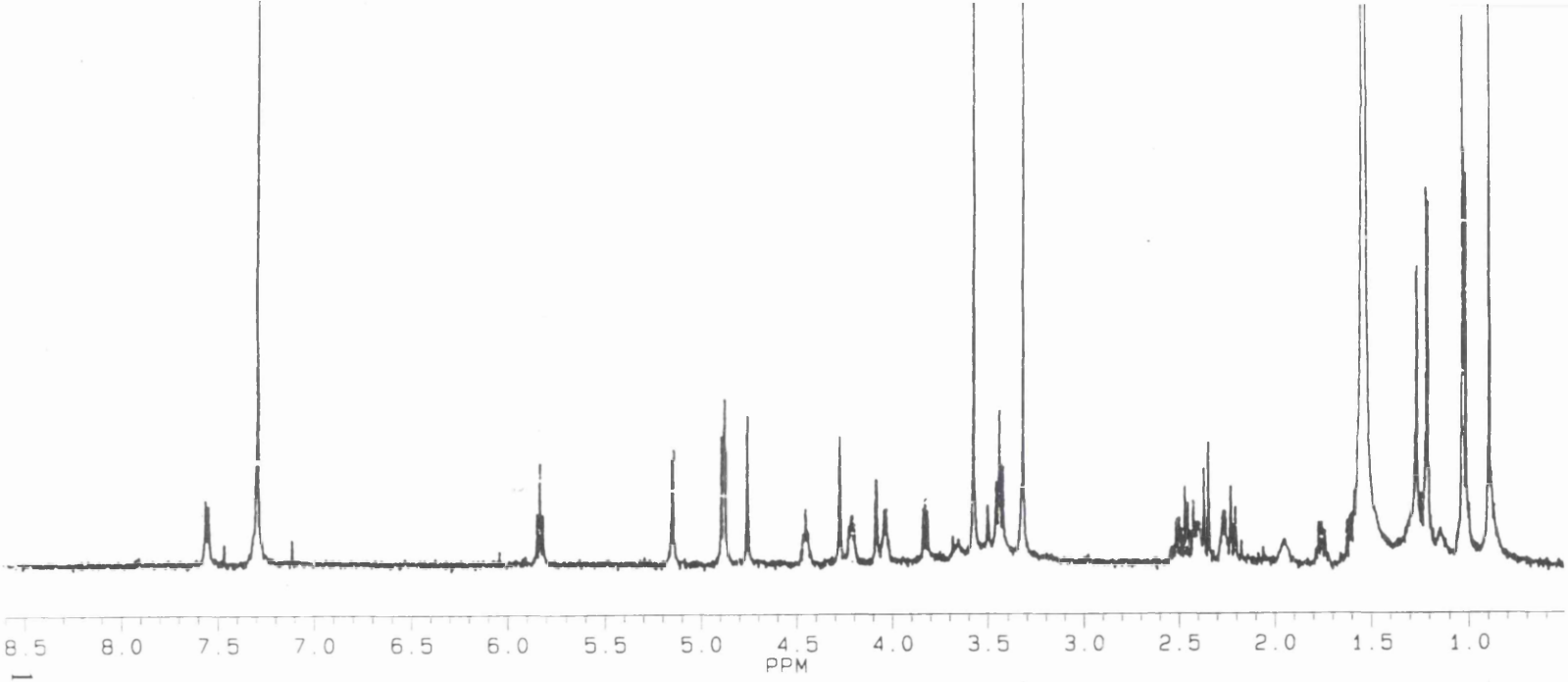
MM2: 12.0 Kcal/mole

E

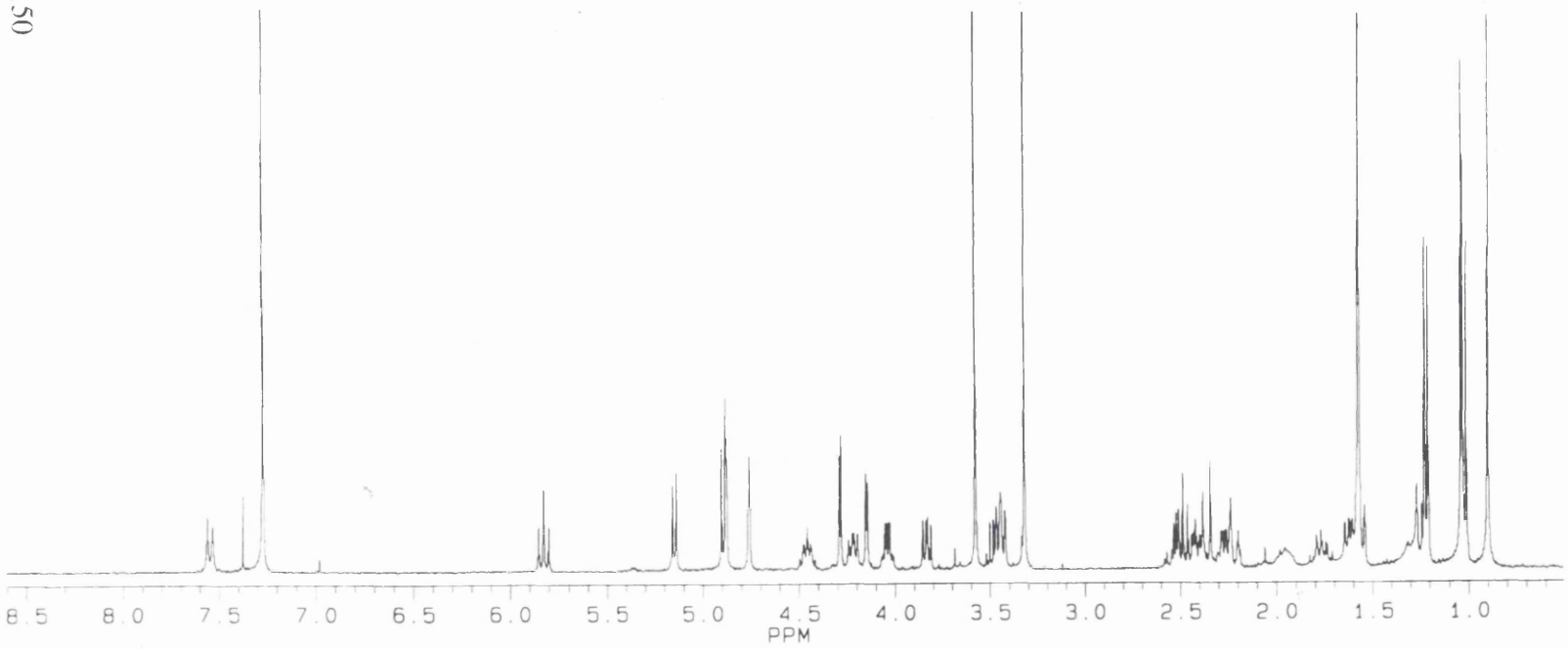


Appendix C ^{1}H and ^{13}C NMR spectra of synthetic theopederin D (1.1d)





^{1}H NMR spectra (600 MHz)
Natural Theopederin D



^{1}H NMR spectra (360 MHz)
Synthetic Theopederin D

12.008
14.115
17.979
22.645
27.957
28.702
31.581
33.300
34.950
41.260
48.484
61.709
69.523
71.552
73.632
76.069
76.681
77.000
77.202
77.318
79.491
86.534
99.807
111.049
144.975
172.273
177.528
ppm
OMe
OMe
OH
O
H
H
O
O
O
O
O
O
19
15
10
7
3

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Summary of Synthetic Route to Theopederin D